IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

VISION BIOSYSTEMS (USA) TRADING, INC., Plaintiff, v. VENTANA MEDICAL SYSTEMS, INC., Defendant.	CIVIL ACTION NO. 03-CV-10391-GAO
VENTANA MEDICAL SYSTEMS, INC. Plaintiff, v. VISION BIOSYSTEMS, INC., Defendant.	CIVIL ACTION NO. 05-CV-10614-GAO

DECLARATION OF ROGER J. CHIN IN SUPPORT OF VENTANA'S OPPOSITION TO VISION'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT BASED ON COLLATERAL ESTOPPEL

I, Roger J. Chin, declare as follows:

1. I am a member of the law firm of Wilson Sonsini Goodrich & Rosati, counsel to defendant Ventana Medical Systems, Inc. The following matters are true of my own personal knowledge.

2. Attached as Exhibit A is a true and correct copy of an Order and Opinion on Motion, filed in *Ventana Medical Systems, Inc. v. BioGenex Laboratories, Inc.*, Case No. CV 03-92 TUC RCC (D. Ariz.), on August 29, 2005.

3. Attached as Exhibit B is a true and correct copy of a Stipulation for Entry of Order Granting Judgment of Noninfringement, filed in *Ventana Medical Systems, Inc. v. BioGenex Laboratories, Inc.*, Case No. CV 03-92 TUC RCC (D. Ariz.), on September 23, 2005.

4. Attached as Exhibit C is a true and correct copy of an Order entering an appealable final judgment, filed in *Ventana Medical Systems, Inc. v. BioGenex Laboratories, Inc.*, Case No. CV 03-92 TUC RCC (D. Ariz.), on October 6, 2005.

5. Attached as Exhibit D is a true and correct copy of a Notice of Appeal, filed in *Ventana Medical Systems, Inc. v. BioGenex Laboratories, Inc.*, Case No. CV 03-92 TUC RCC (D. Ariz.), on October 6, 2005.

6. Attached as Exhibit E is a true and correct copy of a letter from me to Mr. Figg and Ms. Leff, counsel for plaintiff Vision BioSystems (USA) Trading, Inc., sent by facsimile and dated August 30, 2005.

7. Attached as Exhibit F is a true and correct copy of the cover page of the transcript to the deposition of Ross Barrow, taken in this action on September 6, 2005.

8. Attached as Exhibit G is a true and correct copy of a letter from Mr. Figg to Mr. Shulman, counsel for defendant Ventana Medical Systems, Inc., dated October 6, 2005.

9. Attached as Exhibit H is a true and correct copy of U.S. Patent No. 6,352,861.

10. Attached as Exhibit I is a true and correct copy of an Amendment in Patent Application No. 07/924,052, dated May 3, 1994.

11. Attached as Exhibit J is a true and correct copy of an Amendment in Patent Application No. 09/452,309, dated June 26, 2001.

12. Attached as Exhibit K is a true and correct copy of a letter from Mr. Hage, paralegal for plaintiff Vision BioSystems (USA) Trading, Inc., to Ms. Stafford, counsel for defendant Ventana Medical Systems, Inc., dated September 26, 2005.

I declare under penalty of perjury that the foregoing is true and correct. Executed on October 21, 2005, at San Francisco, California.

/s/ Roger J. Chin
Roger J. Chin

UNITED STATES DISTRICT COURT

DISTRICT OF ARIZONA

VENTANA MEDICAL SYSTEMS, INC., Plaintiff, vs. BIOGENIX LABORATORIES, INC., Defendant	CASE NO.: CV 03-92 TUC RCC ORDER and OPINION on MOTION

Pending before the Court are 1) Plaintiff's Claim Construction Brief of the U.S. Patent No. 6,352,861 ('861); and 2) Defendant's Claim Construction Brief of the '861 Patent. On February 11, 2003, Plaintiff Ventana Medical Systems, Inc. ("Ventana") brought this action against Defendant BioGenix Laboratories, Inc. ("BioGenix") alleging infringement of U.S. Patent No. 6,352,861 ('861). The issue before the Court is the interpretation of certain claim language of '861 Patent. The parties briefed their respective positions on claim construction, and the Court held a *Markman* hearing on August 11, 2005. This Memorandum Opinion presents the Court's construction of the disputed terms and phrases.

I. BACKGROUND

Ventana's patent is for an automated immunohistochemical staining device ("autostainer"), which is used for molecular analysis of tissue samples to diagnose cancer and disease. In particular, this patent involves an autostainer that has a carousel reagent support for bar coded reagent containers, a carousel slide support for bar coded slides directly under the carousel reagent support, a bar code reader to identify and locate reagents and slides, and a computer that receives information and coordinates the steps to stain the slide.

Ventana alleges infringement of independent claims 1 and 5, and dependent claims 3, 6, and 8. Both independent claims 1 and 5 recite "[a] method of dispensing reagent onto a slide." Claim 1 recites:

> 1. A method of dispensing reagent onto a slide, the method of comprising the steps of:
>
> [a] providing at least one reagent container;
>
> [b] providing at least one slide of a slide support;
>
> [c] automatically identifying the reagent container using a computer;
>
> [d] automatically determining whether reagent in the reagent container should be *dispensed* onto the slide; and
>
> [e] *dispensing* the reagent in the reagent container onto the slide based on the determination of whether the reagent in the reagent container should be *dispensed* on the slide,
>
> [f] wherein the step of automatically determining whether reagent in the reagent container should be *dispensed* on the slide includes the steps of:
>
> [g] providing a bar code reader;
>
> [h] reading a slide bar code placed on the slide using the bar code reader thereby acquiring slide information indicating reagent to be applied to the slide; and
>
> [i] sending the slide information to the computer

Additionally, Claim 5 recites:

5. A method of dispensing reagents onto a slide, the method comprising the steps of:

[a] providing a plurality of reagent containers in a reagent support, each of the reagent containers having a reagent barcode;

[b] providing at least one slide on a slide support, the slide having a bar code;

[c] providing a bar code reader

[d] reading the bar codes on the reagent containers;

[e] determining reagents in the reagent containers based upon the reading of the bar codes on the reagent containers;

[f] reading the slide bar code on the at least one slide;

[g] determining a sequence of reagents to be applied on the at least one slide based upon the reading of the slide bar code on the slide; and

[h] *dispensing* the reagents in the reagent containers based upon the sequence of reagents to be applied.

After hearing and reviewing the parties' arguments, the Court finds the main dispute centers on the interpretation of "dispensing" and whether it has a narrowed meaning limited to "direct dispensing," excluding the "sip and spit" dispensing employed by the Defendant's product. The other issues before the court include the construction of the claim term "slide," and determining whether to impose a sequence limitation such that the reagent container bar code is read before the slide bar code.

II. THE LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

As a matter of law, the exclusive duty before the court is the construction of disputed claim language of the patents. *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 970 (Fed. Cir. 1995). To resolve disputed claims, "the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification, and if in evidence, the prosecution history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir.

1996).

The claims themselves define the limits of the patented invention and the right to exclude, while the specification and relevant prosecution history serve to understand the language in the claims. *Markman*, 52 F.3d at 980. The specification, or written description of the invention, acts like a dictionary by explaining the invention and defining terms used in the claims. *Markman*, 52 F.3d at 979. The claims "must be read in view of the specification." *Id.* The specification is "the single best guide to the meaning of a disputed term." *Vitronics Corp.*, 90 F.3d at 1582. The prosecution history, if in evidence, is also a significant tool in claim construction because it contains a complete record of the proceedings before the Patent and Trademark Office, including cited prior art not covered in the claims and statements by the patentee disclaiming certain interpretations. *Vitronics*, 90 F.3d at 1582.

Claim construction analysis begins with the patent claims. *Id.* There is a heavy presumption that claim terms carry their ordinary meaning as understood by one of ordinary skill in the art. *CSS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002); *see Vitronics*, 90 F.3d at 1582. This presumption can be rebutted in four ways. *CSS Fitness, Inc.*, 288 F.3d at 1366-67. First, a claim term may be narrowed from its ordinary meaning if the patentee "acted as a lexicographer" and clearly disclosed a special definition for the disputed claim term in the specification or file history. *Id.* at 1366. Second, the ordinary meaning of a term is rebutted "if the patentee distinguished the term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention." *Id.* at 1367. Third, the claim term does not carry its ordinary meaning if it "'deprive[s] the claim of authority' as to require [the court to] resort to the other intrinsic evidence for a definite meaning." *Id.* (quoting *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985 (Fed. Cir. 1999)). Fourth, according to statutory authority, if the claim is a step- or means-plus-function claim, it will only cover the corresponding step or means disclosed in the specification and equivalents thereto. *CSS Fitness, Inc.*, at 1367.

If the disputed claim term continues to be ambiguous after examining the intrinsic evidence, only then may the court use extrinsic evidence, which includes expert and inventor testimony, dictionaries, and treatises. *Vitronics*, 90 F.3d at 1583. Additionally, the court's use of extrinsic evidence must be used "for the court's understanding of the patent, not for the purpose of varying or contradicting the terms of the claims." *Id*. at 981.

III. DISCUSSION

A. "Dispensing" Means "Direct Dispensing."

Ventana stresses the heavy presumption that claim terms carry their ordinary and customary meaning and defines "dispensing" as "applying the agent." In claim elements 1[e] and 5[h], the step is "dispensing the reagent in the reagent container onto the slide..." BioGenix counter-argues that the figures and specification characterize the claimed invention to limit "dispensing" to "direct dispensing," in which the reagent bottle/container is also the reagent dispenser (rather than having some intermediate transport mechanism to "sip and spit").

The ordinary meaning of the claim term may be narrowed by the specification. *CSS Fitness, Inc.*, 288 F.3d at 1366-67; *see also Telefex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002) (The ordinary and customary meaning of a claim term may be narrowed by "characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope."). On the other hand, the court must avoid impermissibly adding limitations from the specification. *Comark Communications v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998). The court must look at how the specification characterizes the claimed invention: does the specification "refer [] to a limitation only as part of less than all possible embodiments" or does the specification in its entirety "suggest [] that the very character of the invention requires the limitation be a part of every embodiment"? *Alloc, Inc. v. Intn'l. Trade Commission*, 342 F.3d 1361, 1370 (Fed. Cir. 2003).

In *Alloc*, the three asserted patents claim systems and methods of joining floors. *Id.* at

1365. None of these patents explicitly recites a "play[1]" limitation; however, "the claims recite floor system features, ... in which play is necessarily present." *Id.* at 1368. The implications of a "play" limitation in the claim language were supported by the specification, which described the invention as a system in which "play exists" and "teaches that the invention as a whole, not merely a preferred embodiment, provides for play in the positioning of floor panels." *Id.* at 1369. Additionally, all of the figures and embodiments in the specification imply "play" and do not suggest any systems without "play." *Id.* at 1370. Thus, in *Alloc*, the common specification "read as a whole leads to the inescapable conclusion that the claimed invention must include play in every embodiment." *Id. See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1348 (Fed. Cir. 2004) (the common specification shared by three patents led to the "inescapable conclusion" that the claims required communication over a telephone line despite the absence of such limiting claim language); *see SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys. Inc.*, 242 F.3d 1337, 1342 (Fed. Cir. 2001) (the common specification shared by three patents led to the "inescapable conclusion" that the claims required coaxial lumens despite the absence of such limiting claim language).

The case here is similar to *Alloc*. The asserted claims in the '861 patent do not explicitly recite "direct" dispensing; however, the context of the claim term "dispensing" supports the narrow construction that it means "direct dispensing." *See Phillips v. AWH Corporation*, 415 F.3d 1303, (Fed. Cir. 2005) ("[T]he claims themselves provide substantial guidance as the meaning of particular claim terms...To begin with, the context in which a term is used in the asserted claim can be highly instructive.") The claim language necessitates "direct dispensing" by stating that the reagent *in* the reagent container is dispensed *onto* the slide, meaning the reagent is dispensed directly from the reagent container. ('861 patent claim elements 1[e], 5[d], 5[h].

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[1] "play" is a space between a locking groove on a first panel and the locking element of a panel adjacent to the first panel; *Alloc*, 342 F.3d at 1367.

Additionally, like *Alloc*, the implication of a "direct dispensing" limitation is supported by the written description and the figures, which also strongly suggests that the reagent is directly dispensed onto the slide from the reagent container. Figure 1 of the '861 patent illustrates the front-right view of the autostainer used to perform the claimed method. In Figure 1, the reagent carousel supports inverted reagent containers directly above the slide carousel. The specification discloses that in Figure 1, "[t]he carousel is rotated... to a position placing a selected reagent bottle in the reagent delivery position under the air cylinder reagent delivery actuator *over a slide to be treated with reagent.*" (col. 6, lines 54-57). Figure 11 of '861 patent illustrates the top view of the slide support carousel of the autostainer and Figure 15 illustrates the cross-sectional view of the reagent receiving station.

In both figures, the reagent delivery actuator and the *inverted* reagent bottle are positioned directly above the slide. *See* col. 9, lines 24-26 ("Air cylinder reagent delivery actuator supported by support arm, contacts reagent bottle, directly over slide."). In this position, the autostainer applies pressurized air to the cylinder and a rod moves downward against a reagent container, col. 11, lines 40-43. As a result, the reagent container moves downward and emits a precise volume of a reagent liquid, which falls through a passageway onto the slide. Col. 11, lines 43-45; col. 12, lines 20-22. Thus, the specification and figures lead to the "inescapable conclusion that the reagent is directly dispensed (without any intermediate transferring device) from an inverted reagent container onto the slide. All of the relevant figures and embodiments in the specification imply "direct dispensing" and do not suggest any alternative dispensing method. Thus, the specification shows that "the invention as a whole[2]" provides for direct dispensing onto the slide. Essentially, the specification in its entirety "leads to the inescapable conclusion that the claimed invention must include [direct dispensing] in every embodiment."

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[2] *Alloc*, 342 F.3d at 1369

B. The clear and unmistakable prosecution disclaimer of "sip and spit" dispensing from the parent '052 application attaches to the same "direct dispensing" claim limitation in the '861 patent.

In the prosecution of a previous parent application (Application No. 07/924,052 ('052)), Ventana disclaimed "sip and spit" dispensing from the claim term "direct dispensing." In "sip and spit" dispensing, the reagent container and sample slide(s) are side-by-side. Some transport mechanism (i.e. micropipette or probe, essentially a straw-like structure) "sips" the reagent from the reagent container by suction and then moves over to the slide and "spits," or releases, the reagent onto the slide. Ventana's '861 patent claims are distinguishable from those in the '052 application because it only recites "dispensing." Ventana argues that the prosecution disclaimer from the parent application cannot apply to the '861 "dispensing" claims. BioGenix argues that the "sip and spit" disclaimer does apply and limits the scope of the '861 patent.

There is a heavy presumption in claim construction that claim terms be interpreted in favor of their ordinary and customary meaning. *CCS Fitness*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). However, if the patentee "unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of surrender." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003). The doctrine of prosecution disclaimer prohibits patentees from "recapturing through claim interpretation specific meanings disclaimed during prosecution." *Id* at 1323. In other words, the claim may not be interpreted in a certain way to obtain the patent and then interpreted differently to allege infringement. *Southwall Technologies,Inc. v. Cardinal Ig. Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). The prosecution disclaimer serves as a public notice and protects reliance on clear statements during prosecution. *Omega*, 334 F.3d at 1324. But in order to balance the patentee's right to seek broad coverage with the public notice function of disclaimers, the Federal Circuit requires "clear and unmistakable" disavowal during prosecution to allow such statements to limit the scope of the claim. *Id.* at 1325.

In particular, a disclaimer made during the prosecution of ancestor patent applications may attach as long as the prosecution disclaimer is directed to a common claim limitation. *Id.* at 1333. *See Advanced Caridovascular Sys., Inc. v. Medtronis, Inc.* 265 F.3d 1294, 1305 (Fed. Cir. 2001) ("The prosecution history of a related patent can be relevant if, for example, it addresses a limitation in common with the patent in suit."); *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999) ("the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contains the same claim limitation."); *Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1300 (Fed. Cir. 1999) ("the prosecution of a parent application may limit the scope a later application using the same claim term."). Thus, narrowing interpretations and disclaimers made during the prosecution of a parent application may attach to subsequent continuation applications. *Omega*, 334 F.3d at 1333-34.

Here, Ventana made a clear and unmistakable disclaimer of the "sip and spit" dispensing method directed toward the claim term "direct dispensing" in the '052 parent application. With respect to the direct dispensing claim limitation, the Patent and Trademark Office rejected Claims 1-3 and 5-6 of the '052 application as being unpatentable[3] over Watake et al. in view of Assmann et al[4]. Office Action of November 29, 1993, BGNX 2197. The '052 application was rejected because "[i]t would have been obvious to one having ordinary skill in the art to replace the reagent containers of Wakatake e al. with the primary vessels as taught by Assman et al.

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[3] Claims 1-3 and 5-6 were rejected for obviousness under 35 U.S.C. § 103:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

[4] Watake et al. discloses an automatic analyzer that has a reagent carousel containing reagent containers. BGNX 2197. Assman et al. discloses an automatic analyzer having a moveable primary vessel containing the reagent that is directly passed to a sample. BGNX 2197.

thereby eliminating the transfer device in order to avoid cross contamination." *Id.* In response, the patentee submitted an amendment, stating:

> Even in the unlikely event that Wakatake and Assman were successfully combined into one system[5], the resulting system would still lack the present invention's novel capability to dispense reagent "directly to a sample" as set for in Applicants' Claim 1, at line 16.Amendment dated April 29, 1994, BGNX 2213.

Claim 1 of the '052 application recites:

> 1. A biological reaction apparatus for dispensing a selected reagent *directly to a sample*, said biological reaction apparatus having:
>
> ...drive means, engaging the reagent carousel and operatively coupled to said homing and indexing means, for rotating the reagent carousel and positioning a preselected reagent container support in a reagent supply zone wherein said reagent supply zone is oriented so that a reagent in a container in said preselected reagent container support is *dispensable directly to a sample*.

'052 Application, BGNX 2083. Exemplary reagent carousel and reagent supply zone encompassed by Applicants' Claim 1 are shown in Figures 1, 2, 3, 15 and 16 of the application. Amendment, BGNX 2215. These figures show that the reagent carousel is positioned above the samples and the reagent containers are inverted to dispense the reagent directly to the sample. *Id*. The patentee disclaims Wakatake by stating:

> In contrast, Wakatake et al teaches reagent tables positioned side-by-side with a reaction table (Wakatake et al, Figure 2). This side by side configuration precludes dispensing of the reagent "directly to the sample" or the incorporation

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[5] Neither Wakatake nor Assman teach or suggest the combination of the two references... the two systems involve incompatible referencing and indexing systems, with Wakatake teaching variable reagent container and sample positions, while Assman depends on stationary reagent container and sample positions...

> of a "reagent delivery zone" as set for in Claim 1 of the present invention. The Wakatake side by side configuration requires an additional device, a reagent pipetting device, to transfer the reagent between tables and mediate the dispensing of reagent to the sample. The reagent pipetting device is used to suck up an aliquot of reagent from a reagent container on one of at least two reagent tables, pivot so that the pipetting tube of the device is held just above a selected reaction vessel on a separate reaction table, and dispense the aliquot of reagent to the vessel (Wakatake at Col. 4, line 42- Co. 5, line 10). Such devices are referred to in the trade as 'sip and spit' devices."

Id. at 2216. Thus the patentee made a "clear and unmistakable" disclaimer of the "sip and spit method" directed toward Claim 1 and Figures 1, 2, 3, 15 and 16 of '052 application.

The clear and unmistakable disclaimer of the "sip and spit" dispensing from the '052 parent application attaches to the '861 "dispensing" limitation because there is a common claim limitation to which the disclaimer is directed: "direct dispensing." The court has already construed the claim term "dispensing" in the '861 patent to mean "direct dispensing" and thus, the '052 application and '861 patent have the same claim limitation. The "sip and spit" disclaimer may properly attach to the '861 patent (direct) dispensing limitation.

C. The Reagent Container and Slide Bar Code Reading Steps Occur in Any Order.

Based on the "natural language of the claims" and the Examiner's Reasons for Allowance[6], BioGenix argues that the claims should be construed to include a sequence limitation in which a bar code reader first reads the reagent bar codes, then reads the slide bar

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[6] BioGenix cited the Examiner's Reasons for Allowance, which indicated some order:

> ...Wherein the apparatus provides a barcode reader for reading the bar codes on the reagent containers, determining reagents in the reagent containers based on the reading of the bar codes. *Thereafter*, the barcode reader reading the slide bar codes and determining the sequence of reagent to be applied on the slides base[d] upon the reading of the slide bar codes. *Lastly*, dispensing reagents in the reagent containers based upon the sequence of reagents to be applied.

However, according to the current version of the Manual of Patent Examining Procedure (MPEP), the patentee's failure to respond/object to the Examiner's Reasons for Allowance is not equivalent to acquiescence:

> The failure of applicant to comment on the examiner's statement of reasons for allowance should not be treated as acquiescence to the examiner's statement. Any inference or presumption are to be determined on a case-by-case basis by a court reviewing the patent, the USPTO examining the patent in a reissue application or a reexamination proceeding, the Board of Patent Appeals and Interference reviewing the patent in an interference proceeding, etc.

Thus, the court will not consider the Examiner's Reasons for Allowance as evidence of a sequence limitation.

codes, the staining run begins and reagents are dispensed. Ventana counters that the claims themselves do not impose an explicit limit on the order of steps.

In *Interactive Gift Express, Inc. v. CompuServe Inc.*, the Federal Circuit held that "[u]nless the steps of a method actually recite an order, the steps are not ordinarily construed to require one.[7]" 256 F.3d 1323, 1342 (Fed. Cir. 2001). However, the Federal Circuit continues to state that method steps can also implicitly require performance of the steps in the order written. *Id.* In *Altiris, Inc. v. Symantec Corp.*, the Federal Circuit clarified its decision in *Interactive* and stated a two-part test for determining if the claimed steps must be performed in the written order when the claim does not explicitly recite an order. 318 F.3d 1363, 1369 (Fed. Cir. 2003).

First, the court must look to the logic and grammar of the claim language to determine if the steps must be performed in the order written. *Id. See, e.g., Loral Fairchild Corp. v. Sony Electronics Corp.*, 181 F.3d 1313, 1321 (Fed. Cir. 1999) (the claim language indicated a sequence limitation because a subsequent step required the completion of a prior step); *Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1375-76 (Fed. Cir. 1998) (the claim language indicated a sequence limitation because each subsequent step made a logical reference indicating the prior step had been completed). Second, if the claim language is not indicative of a sequence limitation, the court must look to the rest of the specification to determine whether the specification directly or implicitly requires such a limitation. *Altiris*, 318 F.3d at 1369. If the specification also fails to require an implicit or explicit sequence limitation, the steps in the claim will not be construed as requiring performance of the steps in the order written.

Here, the claim language does not explicitly or implicitly require a specific order of the steps regarding reading the reagent bar code and slide bar code. All of the steps in the asserted claims do not explicitly indicate an order with language such as "first," "second," "last," etc. Additionally, the logic and grammar of the claimed steps do not require that the bar code reader read the reagent container bar code before the slide bar codes. In Claim 1, the reagent container

[7] claim language that "actually reciting an order," or explicitly reciting an order, uses signal words such as "first," "second," "next," "lastly"

may be identified 1[c] before or after the determination of whether the reagent should be dispensed 1[d], which includes the slide bar code reading step 1[h]. In Claim 5, the bar code reader 5[c] may read the reagent container bar code 5[d] before or after reading the slide bar code 5[f].

In contrast, the logic and grammar of other claim elements in Claims 1 and 5 require a sequence limitation based on language such as "based on/upon" and logical references to completion of a prior step. The following steps in Claim 1 occur in this order: [d], [f], [g], [h], [i], [e][8]; in Claim 5, there are two set of steps that have a sequence limitation, the sets being of any order: [d], [e][9] and [f], [g], [h][10].

The court then must turn to the specification to determine whether the reagent bar code must be read before the slide bar code. BioGenix cites the following in the specification as indicating a particular sequence: *At the beginning* of a slide treatment operation, the reagent carousel is rotated past the bar code reader, and the bar code on each reagent bottle is scanned. Col. 12, lines 31-39. Although the terms "At the beginning" indicate when the bar code reader reads the reagent bar code with respect to the "slide treatment operation," it does not explicitly or implicitly indicate when the bar code reader reads the reagent bar code with respect to reading the slide bar code. BioGenix does not provide sufficient evidence in the specification explicitly

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[8] [d] automatically **determining whether reagent in the reagent container should be dispensed onto the slide**; and
[f] wherein the step of automatically **determining whether reagent in the reagent container should be dispensed on the slide** includes the steps of:
[g] providing a **bar code reader**;
[h] **reading a slide bar code** placed on the slide using the bar code reader thereby **acquiring slide information** indicating reagent to be applied to the slide; and
[i] sending the **slide information** to the computer
[e] dispensing the reagent in the reagent container onto the slide **based on the determination of whether the reagent in the reagent container should be dispensed on the slide**,

[9] [d] **reading the bar codes on the reagent containers**;
[e] determining reagents in the reagent containers **based upon the reading of the bar codes on the reagent containers**;

[10] [f] **reading the slide bar code** on the at least one slide;
[g] **determining a sequence of reagents to be applied** on the at least one slide **based upon the reading of the slide bar code on the slide**; and
[h] dispensing the reagents in the reagent containers based upon the **sequence of reagents to be applied**.

or implicitly requiring the reagent bar codes to be read before the slide bar codes. Thus, according to *Altiris*, the reagent bar code may be read before or after the slide bar code.

D. "Slide" Means a Plain Microscope Slide.

Ventana argues that the term "slide" in claim elements 1[b] and 5[b] should be interpreted by its plain meaning to be an ordinary microscope slide ("a thin glass plate or other material on which an object is placed for microscopic examination"). BioGenix argues that the term "slide" also means "sample container," based upon the specification which states, "The apparatus preferably has bar code readers positioned to read bar codes on the sample containers or slides and on the reagent containers," Col. 2, lines 60-62.

There is a heavy presumption in claim construction that claim terms be interpreted in favor of their ordinary and customary meaning. *CCS Fitness*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). The words of the claims are given their "ordinary and customary meaning" unless a "special definition of the term is clearly stated in the patent specification or file history." *Vitronics Corp.*, 90 F.3d at 1582. For example, departure from the ordinary and customary meaning of slide may be necessary if "a patentee [has chosen] to be his own lexicographer and use terms in a manner other than their ordinary meaning." *Id.* However, the court must be wary of improperly reading a limitation into the claim from the specification. *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998).

BioGenix's reference to "sample containers or slides" does not indicate that sample containers and slides are the same thing, rather the "or" indicates they are different. The specification does not specifically define "slide" or indicate that slide is intended to have a new meaning. The specification supports this conclusion because it refers to a flat plate with edges. *See, e.g.* "slid surface," Col. 4, line 18; "longitudinal edge of the slide" and "distal edge of the slide," Col. 4, lines 56-57. BioGenix counters Ventana's construction by pointing to the inventor's depositions made in other litigation over the '861 patent where they equate a slide to a micro-titer plate (a slide with a well in it to hold fluid), sample container, and/or a test tube. *See*

Exhibits 18 at 41 and 19 at 97. However, expert testimony, or extrinsic evidence (evidence outside of the claim, specification, and prosecution history) is relied on only when "the claim language remains genuinely ambiguous after consideration of the intrinsic evidence." *Bell & Howard Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1997). Here, after reviewing the intrinsic evidence, it is clear that slide carries its ordinary meaning as a microscope slide and the court construes it as such.

E. The Steps in the Claims Are Not Step-Plus-Function Limitations.

BioGenix argued in their brief that the asserted claims were in step-plus-function format and subject to 35 U.S.C. § 112, ¶6[11] which limits the claimed function by the corresponding step or act in the specification. During the *Markman* hearing, BioGenix did not argue this point, conceding that the argument was weak and not necessary to limit "dispensing" to the "direct dispensing" acts described in the specification.

The language "steps of" in the disputed method claim elements 1[c], 1[d], 1[e], 3[a], 5[e], 5[g], 5[h], 6[a] does not invoke 35 U.S.C. § 112, ¶ 6. In the application of § 112 ¶6 to method claims, the statutory term "steps" refers to "the generic description of elements of a process, and the term "acts" [refers] to the implementation of such steps." *O.I. Corp. v. Tekmar Co. Inc.*, 115 F.3d 1576, 1583 (Fed. Cir. 1997). The statute applies only when the claim recites the steps plus function without reciting the acts supporting the function[12]. *Id.* The tradeoff for using functional expressions without reciting all possible acts in the claim is limiting the claim to the corresponding acts specified in the written description and equivalents thereof. *Id.*

---

[11] 35 U.S.C. § 112, ¶ 6:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

[12] Step-plus-function applies when:

1) the claim recites **a step** and **a function**; and
2) the claim **does not recite an act** corresponding to the step-plus-function

In addition, in *Cardiac Pacemakers*, the Federal circuit held that § 112 ¶6 should not be applied to a clause which only recites a step in a method claim and does not use the "steps for" language. 381 F.3d 1371, 1382 (Fed. Cir. 2004). The Federal Circuit Court stated, "[m]ethod claims necessarily recite the steps of the method" and the language "the method comprises the steps of" does not change the subsequent claimed steps into step-plus-function form under § 112 ¶6. *Id.* In fact, the absence of "steps for" language creates the presumption that the claimed steps are *not* in step-plus-function form. *Id.* Furthermore, the Federal Circuit Court disregarded the lower court's concern that the claimed steps would be interpreted too broadly without the limitations of § 112 ¶6, stating that "[a] claim limitation is always construed in light of the specification, whatever the form of the claim." *Id.* at 1381.

Given that the asserted claims do not use the "steps for" language and the claimed elements are written as steps in a method claim, or acts, rather than in purely functional terms, the court will not impose step-plus-function limitations in the asserted claims.

CONCLUSION

For the reasons stated in the court's Memorandum on this same date, the disputed claim terms of the '861 patent shall be construed as set forth in the court's Order of this same date.

IT IS HEREBY ORDERED that:

1. The term "**DISPENSING**" is construed to mean "**DIRECT DISPENSING**."
2. The prosecution disclaimer of "**SIP AND SPIT**" dispensing from the parent '052 application attaches to the '861 patent and further **narrows the construction of the term "DISPENSING" by excluding "SIP** AND SPIT DISPENSING" from its meaning.
3. The bar code reader may read the reagent container bar code and the slide bar code in any order.

4. The term "**SLIDE**" is construed to mean "**PLAIN MICROSCOPE SLIDE**."

5. **STEP-PLUS-FUNCTION** limitations **do not apply** to the asserted claims of the '861 Patent.

Dated this 23rd day of August, 2005.

Raner C. Collins
United States District Judge

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Attorneys for Defendant

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

VETANA MEDICAL SYSTEMS, INC.,

Plaintiff,

v.

BIOGENEX LABORATORIES, INC.,

Defendant.

No. **CIV 03-92 TUC RCC**

STIPULATION FOR ENTRY OF ORDER GRANTING JUDGMENT OF NONINFRINGEMENT

This is a lawsuit for the alleged infringement of U.S. Patent No. 6,352,861 ("the '861 patent"). Plaintiff Ventana Medical Systems, Inc. ("Ventana") has asserted that defendant BioGenex Laboratories, Inc. ("BioGenex") infringes claims 1, 2, 3, 5, 6 and 8 of the '861 patent.

On August 29, 2005, the Court issued its Order and Opinion on Motion (Docket No. 234) ("Markman Order"), construing certain terms of the asserted claims. Specifically, the Court concluded:

1. The term "DISPENSING" is construed to mean "DIRECT DISPENSING."

2. The prosecution disclaimer of "SIP AND SPIT" dispensing from the parent '052 application attaches to the '861 patent and further narrows the construction of the term "DISPENSING" by excluding "SIP AND SPIT DISPENSING" from its meaning.

While Ventana objects to the foregoing claim constructions, Ventana has concluded that the foregoing claim constructions preclude a finding of infringement. *See York Prods., Inc. v. Central Tractor Farm & Family Center*, 99 F.3d 1568, 1571 (Fed. Cir. 1996). Accordingly, to avoid needless expenditure of the resources of the parties and the Court, the parties stipulate without prejudice to either on appeal that an appealable final judgment of noninfringement in the form attached shall be entered forthwith in favor of BioGenex, as follows:

A. The accused products in this litigation do not perform "direct dispensing" as that term is used in the Court's Markman Order. The accused products dispense reagent by means of "sip and spit dispensing" as that term is used in the Court's Markman Order.

B. The Court's construction of the term "dispensing" in the Markman Order precludes a finding of infringement of claims 1, 2, 3, 5, 6 and 8 of the '861 patent. The accused products do not infringe claims 1, 2, 3, 5, 6 and 8 of the '861 patent by virtue of findings 1 and 2 of the Court's Markman Order and by virtue of the fact that the accused products do not practice "direct dispensing."

C. Either party shall be entitled to supplement pursuant to the Court's Order of June 9, 2005. Defendant shall be entitled to apply for attorney's fees, but the Court's order expresses no opinion as to whether or not an award of attorney's fees would be appropriate.

D. The parties shall have the same right of appeal they would have had in the event a final judgment of noninfringement had been entered following either a dispositive ruling by the Court or a jury verdict. The intent of this stipulation is to produce an appealable final judgment. *See Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1371 (Fed. Cir. 1998).

E. Except as provided herein, all pending motions are denied without prejudice as moot, but may be reinstated at the request of the moving party should the case be remanded to this Court for further proceedings.

DATED this 16th day of September, 2005.

QUARLES & BRADY
STREICH LANG LLP

WILSON SONSINI GOODRICH & ROSATI

By: _____
Roger J. Chin (*pro hac vice*)

Attorneys for Plaintiff
Ventana Medical Systems, Inc.

LEONARD FELKER ALTFELD
GREENBERG & BATTAILE, P.C.

By: _____

Attorneys for Defendant
BioGenex Laboratories, Inc.

ORIGINAL AND ONE COPY filed
this ~~16th~~ 23rd day of September, 2005:

Clerk, U.S. District Court
405 West Congress
Tucson, Arizona 85701

E. Campbell

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

VETANA MEDICAL SYSTEMS, INC.,

Plaintiff,

v.

BIOGENEX LABORATORIES, INC.,

Defendant.

No. **CIV 03-92 TUC RCC**

PROPOSED FINAL JUDGMENT OF NONINFRINGEMENT

The Court hereby enters an appealable final judgment of noninfringement in favor of defendant BioGenex Laboratories, Inc. The Court further finds and orders:

A. The accused products in this litigation do not perform "direct dispensing" as that term is used in the Court's Order and Opinion on Motion (Aug. 29, 2005) (Docket No. 234) ("Markman Order"). The accused products dispense reagent by means of "sip and spit dispensing" as that term is used in the Court's Markman Order.

B. The Court's construction of the term "dispensing" in the Markman Order precludes a finding of infringement of claims 1, 2, 3, 5, 6 and 8 of the '861 patent. The accused products do not infringe claims 1, 2, 3, 5, 6 and 8 of the '861 patent by virtue of findings 1 and 2 of the Court's Markman Order and by virtue of the fact that the accused products do not practice "direct dispensing."

C. Either party shall be entitled to supplement pursuant to the Court's Order of June 9, 2005. Defendant shall be entitled to apply for attorney's fees, but this order

expresses no opinion as to whether or not an award of attorney's fees would be appropriate.

D. The parties shall have the same right of appeal they would have had in the event a final judgment of noninfringement had been entered following either a dispositive ruling by the Court or a jury verdict. The intent of this order is to produce an appealable final judgment. *See Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1371 (Fed. Cir. 1998).

E. Except as provided herein, all pending motions are denied without prejudice as moot, but may be reinstated at the request of the moving party should the case be remanded to this Court for further proceedings.

IT IS SO ORDERED.

DATED this ____ day of _____, 2005.

_____
Hon. Raner C. Collins
District Court Judge

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

VENTANA MEDICAL SYSTEMS, INC.,

Plaintiff,

vs.

BIOGENEX LABORATORIES, INC.,

Defendant.

No. 03-92-TUC-RCC

ORDER

The Court hereby enters an appealable final judgment of noninfringement in favor of defendant BioGenex Laboratories, Inc. The Court further **FINDS** and **ORDERS:**

A. The accused products in this litigation do not perform "direct dispensing" as that term is used in the Court's Order and Opinion on Motion (August 29, 2005) (Docket No. 234) ("Markman Order"). The accused products dispense reagent by means of "sip and spit dispensing" as that term is used in the Court's Markman Order.

B. The Court's construction of the term "dispensing" in the Markman Order precludes a finding of infringement of claims 1, 2, 3, 5, 6 and 8 of the '861 patent. The accused products do not infringe claims 1, 2, 3, 5, 6 and 8 of the '861 patent by virtue of findings 1 and 2 of the Court's Markman Order and by virtue of the fact that the accused products do not practice "direct dispensing."

C. Either party shall be entitled to supplement pursuant to the Court's Order of June 9, 2005. Defendant shall be entitled to apply for attorney's fees, but this order

expresses no opinion as to whether or not an award of attorney's fees would be appropriate.

D. The parties shall have the same right of appeal they would have had in the event of a final judgment of noninfringement had been entered following either a dispositive ruling by the Court or a jury verdict. The intent of this order is to produce an appealable final judgment. *See Mantech Envtl. Corp v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1371 (Fed. Cir. 1998).

E. Except as provided herein, all pending motions are denied without prejudice as moot, but may be reinstated at the request of the moving party should the case be remanded to this Court for further proceedings.

IT IS SO ORDERED.

DATED this 4th day of October, 2005.

Rainer C. Collins
United States District Judge

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Attorneys for Plaintiff

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

VENTANA MEDICAL SYSTEMS, INC., Plaintiff, v. BIOGENEX LABORATORIES, INC., Defendant.	No. **CIV 03-92 TUC RCC** **NOTICE OF APPEAL**

Notice is hereby given that plaintiff Ventana Medical Systems, Inc. in the above named case hereby appeals to the United States Court of Appeals for the Federal Circuit from the final judgment entered in this action on October 6, 2005, and all rulings and orders merged therein, including without limitation the Order and Opinion on Motion filed on August 29, 2005 (Docket No. 234) and the Order filed on October 6, 2005 (Docket No. 265).

DATED this 6th day of October, 2005.

QUARLES & BRADY STREICH LANG LLP
One South Church Avenue, Suite 1700
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By: _____
Craig H. Kaufman

Attorneys for Plaintiff
Ventana Medical Systems, Inc.

ORIGINAL FILED ECF
this 6th day of October, 2005:

Clerk, U.S. District Court
405 West Congress
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COPY of the foregoing hand-delivered
this 6th day of October, 2005:

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August 30, 2005

VIA FACSIMILE

E. Anthony Figg, Esq.
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Re: ***Ventana Medical Systems, Inc. v. Vision BioSystems, Inc.*,**
Case No. 05-CV-10614-GAO (D. Mass.)

Dear Tony and Elizabeth:

Attached to this letter please find a copy of an order issued yesterday by the U.S. District Court for the District of Arizona.

Sincerely,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Roger J. Chin

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UNITED STATES DISTRICT COURT

DISTRICT OF ARIZONA

VENTANA MEDICAL SYSTEMS, INC., Plaintiff, vs. BIOGENIX LABORATORIES, INC., Defendant	CASE NO.: CV 03-92 TUC RCC ORDER and OPINION on MOTION

Pending before the Court are 1) Plaintiff's Claim Construction Brief of the U.S. Patent No. 6,352,861 ('861); and 2) Defendant's Claim Construction Brief of the '861 Patent. On February 11, 2003, Plaintiff Ventana Medical Systems, Inc. ("Ventana") brought this action against Defendant BioGenix Laboratories, Inc. ("BioGenix") alleging infringement of U.S. Patent No. 6,352,861 ('861). The issue before the Court is the interpretation of certain claim language of '861 Patent. The parties briefed their respective positions on claim construction, and the Court held a *Markman* hearing on August 11, 2005. This Memorandum Opinion presents the Court's construction of the disputed terms and phrases.

I. BACKGROUND

Ventana's patent is for an automated immunohistochemical staining device ("autostainer"), which is used for molecular analysis of tissue samples to diagnose cancer and disease. In particular, this patent involves an autostainer that has a carousel reagent support for bar coded reagent containers, a carousel slide support for bar coded slides directly under the carousel reagent support, a bar code reader to identify and locate reagents and slides, and a computer that receives information and coordinates the steps to stain the slide.

Ventana alleges infringement of independent claims 1 and 5, and dependent claims 3, 6, and 8. Both independent claims 1 and 5 recite "[a] method of dispensing reagent onto a slide." Claim 1 recites:

> 1. A method of dispensing reagent onto a slide, the method of comprising the steps of:
>
> [a] providing at least one reagent container;
>
> [b] providing at least one slide of a slide support;
>
> [c] automatically identifying the reagent container using a computer;
>
> [d] automatically determining whether reagent in the reagent container should be *dispensed* onto the slide; and
>
> [e] *dispensing* the reagent in the reagent container onto the slide based on the determination of whether the reagent in the reagent container should be *dispensed* on the slide,
>
> [f] wherein the step of automatically determining whether reagent in the reagent container should be *dispensed* on the slide includes the steps of:
>
> [g] providing a bar code reader;
>
> [h] reading a slide bar code placed on the slide using the bar code reader thereby acquiring slide information indicating reagent to be applied to the slide; and
>
> [i] sending the slide information to the computer

Additionally, Claim 5 recites:

5. A method of dispensing reagents onto a slide, the method comprising the steps of:

[a] providing a plurality of reagent containers in a reagent support, each of the reagent containers having a reagent barcode;

[b] providing at least one slide on a slide support, the slide having a bar code;

[c] providing a bar code reader

[d] reading the bar codes on the reagent containers;

[e] determining reagents in the reagent containers based upon the reading of the bar codes on the reagent containers;

[f] reading the slide bar code on the at least one slide;

[g] determining a sequence of reagents to be applied on the at least one slide based upon the reading of the slide bar code on the slide; and

[h] *dispensing* the reagents in the reagent containers based upon the sequence of reagents to be applied.

After hearing and reviewing the parties' arguments, the Court finds the main dispute centers on the interpretation of "dispensing" and whether it has a narrowed meaning limited to "direct dispensing," excluding the "sip and spit" dispensing employed by the Defendant's product. The other issues before the court include the construction of the claim term "slide," and determining whether to impose a sequence limitation such that the reagent container bar code is read before the slide bar code.

II. THE LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

As a matter of law, the exclusive duty before the court is the construction of disputed claim language of the patents. *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 970 (Fed. Cir. 1995). To resolve disputed claims, "the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification, and if in evidence, the prosecution history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir.

1996).

The claims themselves define the limits of the patented invention and the right to exclude, while the specification and relevant prosecution history serve to understand the language in the claims. *Markman*, 52 F.3d at 980. The specification, or written description of the invention, acts like a dictionary by explaining the invention and defining terms used in the claims. *Markman*, 52 F.3d at 979. The claims "must be read in view of the specification." *Id.* The specification is "the single best guide to the meaning of a disputed term." *Vitronics Corp.*, 90 F.3d at 1582. The prosecution history, if in evidence, is also a significant tool in claim construction because it contains a complete record of the proceedings before the Patent and Trademark Office, including cited prior art not covered in the claims and statements by the patentee disclaiming certain interpretations. *Vitronics*, 90 F.3d at 1582.

Claim construction analysis begins with the patent claims. *Id.* There is a heavy presumption that claim terms carry their ordinary meaning as understood by one of ordinary skill in the art. *CSS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002); *see Vitronics*, 90 F.3d at 1582. This presumption can be rebutted in four ways. *CSS Fitness, Inc.*, 288 F.3d at 1366-67. First, a claim term may be narrowed from its ordinary meaning if the patentee "acted as a lexicographer" and clearly disclosed a special definition for the disputed claim term in the specification or file history. *Id.* at 1366. Second, the ordinary meaning of a term is rebutted "if the patentee distinguished the term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention." *Id.* at 1367. Third, the claim term does not carry its ordinary meaning if it "'deprive[s] the claim of authority' as to require [the court to] resort to the other intrinsic evidence for a definite meaning." *Id.* (quoting *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985 (Fed. Cir. 1999)). Fourth, according to statutory authority, if the claim is a step- or means-plus-function claim, it will only cover the corresponding step or means disclosed in the specification and equivalents thereto. *CSS Fitness, Inc.*, at 1367.

If the disputed claim term continues to be ambiguous after examining the intrinsic evidence, only then may the court use extrinsic evidence, which includes expert and inventor testimony, dictionaries, and treatises. *Vitronics*, 90 F.3d at 1583. Additionally, the court's use of extrinsic evidence must be used "for the court's understanding of the patent, not for the purpose of varying or contradicting the terms of the claims." *Id.* at 981.

III. DISCUSSION

A. "Dispensing" Means "Direct Dispensing."

Ventana stresses the heavy presumption that claim terms carry their ordinary and customary meaning and defines "dispensing" as "applying the agent." In claim elements 1[e] and 5[h], the step is "dispensing the reagent in the reagent container onto the slide..." BioGenix counter-argues that the figures and specification characterize the claimed invention to limit "dispensing" to "direct dispensing," in which the reagent bottle/container is also the reagent dispenser (rather than having some intermediate transport mechanism to "sip and spit").

The ordinary meaning of the claim term may be narrowed by the specification. *CSS Fitness, Inc.*, 288 F.3d at 1366-67; *see also Telefex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002) (The ordinary and customary meaning of a claim term may be narrowed by "characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope."). On the other hand, the court must avoid impermissibly adding limitations from the specification. *Comark Communications v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998). The court must look at how the specification characterizes the claimed invention: does the specification "refer [] to a limitation only as part of less than all possible embodiments" or does the specification in its entirety "suggest [] that the very character of the invention requires the limitation be a part of every embodiment"? *Alloc, Inc. v. Intn'l. Trade Commission,* 342 F.3d 1361, 1370 (Fed. Cir. 2003).

In *Alloc,* the three asserted patents claim systems and methods of joining floors. *Id.* at

1365. None of these patents explicitly recites a "play[1]" limitation; however, "the claims recite floor system features, ... in which play is necessarily present." *Id.* at 1368. The implications of a "play" limitation in the claim language were supported by the specification, which described the invention as a system in which "play exists" and "teaches that the invention as a whole, not merely a preferred embodiment, provides for play in the positioning of floor panels." *Id.* at 1369. Additionally, all of the figures and embodiments in the specification imply "play" and do not suggest any systems without "play." *Id.* at 1370. Thus, in *Alloc,* the common specification "read as a whole leads to the inescapable conclusion that the claimed invention must include play in every embodiment." *Id. See Microsoft Corp. v. Multi-Tech Sys., Inc.,* 357 F.3d 1340, 1348 (Fed. Cir. 2004) (the common specification shared by three patents led to the "inescapable conclusion" that the claims required communication over a telephone line despite the absence of such limiting claim language); *see SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys. Inc.,* 242 F.3d 1337, 1342 (Fed. Cir. 2001) (the common specification shared by three patents led to the "inescapable conclusion" that the claims required coaxial lumens despite the absence of such limiting claim language).

The case here is similar to *Alloc*. The asserted claims in the '861 patent do not explicitly recite "direct" dispensing; however, the context of the claim term "dispensing" supports the narrow construction that it means "direct dispensing." *See Phillips v. AWH Corporation,* 415 F.3d 1303, (Fed. Cir. 2005) ("[T]he claims themselves provide substantial guidance as the meaning of particular claim terms...To begin with, the context in which a term is used in the asserted claim can be highly instructive.") The claim language necessitates "direct dispensing" by stating that the reagent *in* the reagent container is dispensed *onto* the slide, meaning the reagent is dispensed directly from the reagent container. ('861 patent claim elements 1[e], 5[d], 5[h].

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[1] "play" is a space between a locking groove on a first panel and the locking element of a panel adjacent to the first panel; *Alloc*, 342 F.3d at 1367.

Additionally, like *Alloc*, the implication of a "direct dispensing" limitation is supported by the written description and the figures, which also strongly suggests that the reagent is directly dispensed onto the slide from the reagent container. Figure 1 of the '861 patent illustrates the front-right view of the autostainer used to perform the claimed method. In Figure 1, the reagent carousel supports inverted reagent containers directly above the slide carousel. The specification discloses that in Figure 1, "[t]he carousel is rotated... to a position placing a selected reagent bottle in the reagent delivery position under the air cylinder reagent delivery actuator *over a slide to be treated with reagent.*" (col. 6, lines 54-57). Figure 11 of '861 patent illustrates the top view of the slide support carousel of the autostainer and Figure 15 illustrates the cross-sectional view of the reagent receiving station.

In both figures, the reagent delivery actuator and the *inverted* reagent bottle are positioned directly above the slide. *See* col. 9, lines 24-26 ("Air cylinder reagent delivery actuator supported by support arm, contacts reagent bottle, directly over slide."). In this position, the autostainer applies pressurized air to the cylinder and a rod moves downward against a reagent container, col. 11, lines 40-43. As a result, the reagent container moves downward and emits a precise volume of a reagent liquid, which falls through a passageway onto the slide. Col. 11, lines 43-45; col. 12, lines 20-22. Thus, the specification and figures lead to the "inescapable conclusion that the reagent is directly dispensed (without any intermediate transferring device) from an inverted reagent container onto the slide. All of the relevant figures and embodiments in the specification imply "direct dispensing" and do not suggest any alternative dispensing method. Thus, the specification shows that "the invention as a whole[2]" provides for direct dispensing onto the slide. Essentially, the specification in its entirety "leads to the inescapable conclusion that the claimed invention must include [direct dispensing] in every embodiment."

---

[2] *Alloc*, 342 F.3d at 1369

B. The clear and unmistakable prosecution disclaimer of "sip and spit" dispensing from the parent '052 application attaches to the same "direct dispensing" claim limitation in the '861 patent.

In the prosecution of a previous parent application (Application No. 07/924,052 ('052)), Ventana disclaimed "sip and spit" dispensing from the claim term "direct dispensing." In "sip and spit" dispensing, the reagent container and sample slide(s) are side-by-side. Some transport mechanism (i.e. micropipette or probe, essentially a straw-like structure) "sips" the reagent from the reagent container by suction and then moves over to the slide and "spits," or releases, the reagent onto the slide. Ventana's '861 patent claims are distinguishable from those in the '052 application because it only recites "dispensing." Ventana argues that the prosecution disclaimer from the parent application cannot apply to the '861 "dispensing" claims. BioGenix argues that the "sip and spit" disclaimer does apply and limits the scope of the '861 patent.

There is a heavy presumption in claim construction that claim terms be interpreted in favor of their ordinary and customary meaning. *CCS Fitness,* 288 F.3d 1359, 1366 (Fed. Cir. 2002). However, if the patentee "unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of surrender." *Omega Eng'g, Inc. v. Raytek Corp.,* 334 F.3d 1314, 1324 (Fed. Cir. 2003). The doctrine of prosecution disclaimer prohibits patentees from "recapturing through claim interpretation specific meanings disclaimed during prosecution." *Id.* at 1323. In other words, the claim may not be interpreted in a certain way to obtain the patent and then interpreted differently to allege infringement. *Southwall Technologies,Inc. v. Cardinal Ig. Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). The prosecution disclaimer serves as a public notice and protects reliance on clear statements during prosecution. *Omega*, 334 F.3d at 1324. But in order to balance the patentee's right to seek broad coverage with the public notice function of disclaimers, the Federal Circuit requires "clear and unmistakable" disavowal during prosecution to allow such statements to limit the scope of the claim. *Id.* at 1325.

In particular, a disclaimer made during the prosecution of ancestor patent applications may attach as long as the prosecution disclaimer is directed to a common claim limitation. *Id.* at 1333. *See Advanced Caridovascular Sys., Inc. v. Medtronis, Inc.* 265 F.3d 1294, 1305 (Fed. Cir. 2001) ("The prosecution history of a related patent can be relevant if, for example, it addresses a limitation in common with the patent in suit."); *Elkay Mfg. Co. v. Ebco Mfg. Co.,* 192 F.3d 973, 980 (Fed. Cir. 1999) ("the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contains the same claim limitation."); *Augustine Med., Inc. v. Gaymar Indus., Inc.,* 181 F.3d 1291, 1300 (Fed. Cir. 1999) ("the prosecution of a parent application may limit the scope a later application using the same claim term."). Thus, narrowing interpretations and disclaimers made during the prosecution of a parent application may attach to subsequent continuation applications. *Omega,* 334 F.3d at 1333-34.

Here, Ventana made a clear and unmistakable disclaimer of the "sip and spit" dispensing method directed toward the claim term "direct dispensing" in the '052 parent application. With respect to the direct dispensing claim limitation, the Patent and Trademark Office rejected Claims 1-3 and 5-6 of the '052 application as being unpatentable[3] over Watake et al. in view of Assmann et al[4]. Office Action of November 29, 1993, BGNX 2197. The '052 application was rejected because "[i]t would have been obvious to one having ordinary skill in the art to replace the reagent containers of Wakatake e al. with the primary vessels as taught by Assman et al.

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[3] Claims 1-3 and 5-6 were rejected for obviousness under 35 U.S.C. § 103:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

[4] Watake et al. discloses an automatic analyzer that has a reagent carousel containing reagent containers. BGNX 2197. Assman et al. discloses an automatic analyzer having a moveable primary vessel containing the reagent that is directly passed to a sample. BGNX 2197.

thereby eliminating the transfer device in order to avoid cross contamination." *Id.* In response, the patentee submitted an amendment, stating:

> Even in the unlikely event that Wakatake and Assman were successfully combined into one system[5], the resulting system would still lack the present invention's novel capability to dispense reagent "directly to a sample" as set for in Applicants' Claim 1, at line 16.Amendment dated April 29, 1994, BGNX 2213.

Claim 1 of the '052 application recites:

> 1. A biological reaction apparatus for dispensing a selected reagent *directly to a sample*, said biological reaction apparatus having:
>
> ...drive means, engaging the reagent carousel and operatively coupled to said homing and indexing means, for rotating the reagent carousel and positioning a preselected reagent container support in a reagent supply zone wherein said reagent supply zone is oriented so that a reagent in a container in said preselected reagent container support is *dispensable directly to a sample*.

'052 Application, BGNX 2083. Exemplary reagent carousel and reagent supply zone encompassed by Applicants' Claim 1 are shown in Figures 1, 2, 3, 15 and 16 of the application. Amendment, BGNX 2215. These figures show that the reagent carousel is positioned above the samples and the reagent containers are inverted to dispense the reagent directly to the sample. *Id.* The patentee disclaims Wakatake by stating:

> In contrast, Wakatake et al teaches reagent tables positioned side-by-side with a reaction table (Wakatake et al, Figure 2). This side by side configuration precludes dispensing of the reagent "directly to the sample" or the incorporation

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[5] Neither Wakatake nor Assman teach or suggest the combination of the two references... the two systems involve incompatible referencing and indexing systems, with Wakatake teaching variable reagent container and sample positions, while Assman depends on stationary reagent container and sample positions...

> of a "reagent delivery zone" as set for in Claim 1 of the present invention. The Wakatake side by side configuration requires an additional device, a reagent pipetting device, to transfer the reagent between tables and mediate the dispensing of reagent to the sample. The reagent pipetting device is used to suck up an aliquot of reagent from a reagent container on one of at least two reagent tables, pivot so that the pipetting tube of the device is held just above a selected reaction vessel on a separate reaction table, and dispense the aliquot of reagent to the vessel (Wakatake at Col. 4, line 42- Co. 5, line 10). Such devices are referred to in the trade as 'sip and spit' devices."

Id. at 2216. Thus the patentee made a "clear and unmistakable" disclaimer of the "sip and spit method" directed toward Claim 1 and Figures 1, 2, 3, 15 and 16 of '052 application.

The clear and unmistakable disclaimer of the "sip and spit" dispensing from the '052 parent application attaches to the '861 "dispensing" limitation because there is a common claim limitation to which the disclaimer is directed: "direct dispensing." The court has already construed the claim term "dispensing" in the '861 patent to mean "direct dispensing" and thus, the '052 application and '861 patent have the same claim limitation. The "sip and spit" disclaimer may properly attach to the '861 patent (direct) dispensing limitation.

C. The Reagent Container and Slide Bar Code Reading Steps Occur in Any Order.

Based on the "natural language of the claims" and the Examiner's Reasons for Allowance[6], BioGenix argues that the claims should be construed to include a sequence limitation in which a bar code reader first reads the reagent bar codes, then reads the slide bar

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[6] BioGenix cited the Examiner's Reasons for Allowance, which indicated some order:

> ...Wherein the apparatus provides a barcode reader for reading the bar codes on the reagent containers, determining reagents in the reagent containers based on the reading of the bar codes. *Thereafter*, the barcode reader reading the slide bar codes and determining the sequence of reagent to be applied on the slides base[d] upon the reading of the slide bar codes. *Lastly*, dispensing reagents in the reagent containers based upon the sequence of reagents to be applied.

However, according to the current version of the Manual of Patent Examining Procedure (MPEP), the patentee's failure to respond/object to the Examiner's Reasons for Allowance is not equivalent to acquiescence:

> The failure of applicant to comment on the examiner's statement of reasons for allowance should not be treated as acquiescence to the examiner's statement. Any inference or presumption are to be determined on a case-by-case basis by a court reviewing the patent, the USPTO examining the patent in a reissue application or a reexamination proceeding, the Board of Patent Appeals and Interference reviewing the patent in an interference proceeding, etc.

Thus, the court will not consider the Examiner's Reasons for Allowance as evidence of a sequence limitation.

codes, the staining run begins and reagents are dispensed. Ventana counters that the claims themselves do not impose an explicit limit on the order of steps.

In *Interactive Gift Express, Inc. v. CompuServe Inc.*, the Federal Circuit held that "[u]nless the steps of a method actually recite an order, the steps are not ordinarily construed to require one.[7]" 256 F.3d 1323, 1342 (Fed. Cir. 2001). However, the Federal Circuit continues to state that method steps can also implicitly require performance of the steps in the order written. *Id.* In *Altiris, Inc. v. Symantec Corp.*, the Federal Circuit clarified its decision in *Interactive* and stated a two-part test for determining if the claimed steps must be performed in the written order when the claim does not explicitly recite an order. 318 F.3d 1363, 1369 (Fed. Cir. 2003).

First, the court must look to the logic and grammar of the claim language to determine if the steps must be performed in the order written. *Id. See, e.g., Loral Fairchild Corp. v. Sony Electronics Corp.*, 181 F.3d 1313, 1321 (Fed. Cir. 1999) (the claim language indicated a sequence limitation because a subsequent step required the completion of a prior step); *Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1375-76 (Fed. Cir. 1998) (the claim language indicated a sequence limitation because each subsequent step made a logical reference indicating the prior step had been completed). Second, if the claim language is not indicative of a sequence limitation, the court must look to the rest of the specification to determine whether the specification directly or implicitly requires such a limitation. *Altiris*, 318 F.3d at 1369. If the specification also fails to require an implicit or explicit sequence limitation, the steps in the claim will not be construed as requiring performance of the steps in the order written.

Here, the claim language does not explicitly or implicitly require a specific order of the steps regarding reading the reagent bar code and slide bar code. All of the steps in the asserted claims do not explicitly indicate an order with language such as "first," "second," "last," etc. Additionally, the logic and grammar of the claimed steps do not require that the bar code reader read the reagent container bar code before the slide bar codes. In Claim 1, the reagent container

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[7] claim language that "actually reciting an order," or explicitly reciting an order, uses signal words such as "first," "second," "next," "lastly"

may be identified 1[c] before or after the determination of whether the reagent should be dispensed 1[d], which includes the slide bar code reading step 1[h]. In Claim 5, the bar code reader 5[c] may read the reagent container bar code 5[d] before or after reading the slide bar code 5[f].

In contrast, the logic and grammar of other claim elements in Claims 1 and 5 require a sequence limitation based on language such as "based on/upon" and logical references to completion of a prior step. The following steps in Claim 1 occur in this order: [d], [f], [g], [h], [i], [e][8]; in Claim 5, there are two set of steps that have a sequence limitation, the sets being of any order: [d], [e][9] and [f], [g], [h][10].

The court then must turn to the specification to determine whether the reagent bar code must be read before the slide bar code. BioGenix cites the following in the specification as indicating a particular sequence: *At the beginning* of a slide treatment operation, the reagent carousel is rotated past the bar code reader, and the bar code on each reagent bottle is scanned. Col. 12, lines 31-39. Although the terms "At the beginning" indicate when the bar code reader reads the reagent bar code with respect to the "slide treatment operation," it does not explicitly or implicitly indicate when the bar code reader reads the reagent bar code with respect to reading the slide bar code. BioGenix does not provide sufficient evidence in the specification explicitly

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[8] [d] automatically **determining whether reagent in the reagent container should be dispensed onto the slide**; and
[f] wherein the step of automatically **determining whether reagent in the reagent container should be dispensed on the slide** includes the steps of:
[g] providing a **bar code reader**;
[h] **reading a slide bar code** placed on the slide using the bar code reader thereby **acquiring slide information** indicating reagent to be applied to the slide; and
[i] sending the **slide information** to the computer
[e] dispensing the reagent in the reagent container onto the slide **based on the determination of whether the reagent in the reagent container should be dispensed on the slide**,

[9] [d] **reading the bar codes on the reagent containers**;
[e] determining reagents in the reagent containers **based upon the reading of the bar codes on the reagent containers**;

[10] [f] **reading the slide bar code** on the at least one slide;
[g] **determining a sequence of reagents to be applied** on the at least one slide **based upon the reading of the slide bar code on the slide**; and
[h] dispensing the reagents in the reagent containers based upon the **sequence of reagents to be applied**.

or implicitly requiring the reagent bar codes to be read before the slide bar codes. Thus, according to *Altiris,* the reagent bar code may be read before or after the slide bar code.

D. "Slide" Means a Plain Microscope Slide.

Ventana argues that the term "slide" in claim elements 1[b] and 5[b] should be interpreted by its plain meaning to be an ordinary microscope slide ("a thin glass plate or other material on which an object is placed for microscopic examination"). BioGenix argues that the term "slide" also means "sample container," based upon the specification which states, "The apparatus preferably has bar code readers positioned to read bar codes on the sample containers or slides and on the reagent containers," Col. 2, lines 60-62.

There is a heavy presumption in claim construction that claim terms be interpreted in favor of their ordinary and customary meaning. *CCS Fitness,* 288 F.3d 1359, 1366 (Fed. Cir. 2002). The words of the claims are given their "ordinary and customary meaning" unless a "special definition of the term is clearly stated in the patent specification or file history." *Vitronics Corp.,* 90 F.3d at 1582. For example, departure from the ordinary and customary meaning of slide may be necessary if "a patentee [has chosen] to be his own lexicographer and use terms in a manner other than their ordinary meaning." *Id.* However, the court must be wary of improperly reading a limitation into the claim from the specification. *Comark Communications, Inc. v. Harris Corp.,* 156 F.3d 1182, 1186 (Fed. Cir. 1998).

BioGenix's reference to "sample containers or slides" does not indicate that sample containers and slides are the same thing, rather the "or" indicates they are different. The specification does not specifically define "slide" or indicate that slide is intended to have a new meaning. The specification supports this conclusion because it refers to a flat plate with edges. *See, e.g.* "slid surface," Col. 4, line 18; "longitudinal edge of the slide" and "distal edge of the slide," Col. 4, lines 56-57. BioGenix counters Ventana's construction by pointing to the inventor's depositions made in other litigation over the '861 patent where they equate a slide to a micro-titer plate (a slide with a well in it to hold fluid), sample container, and/or a test tube. *See*

Exhibits 18 at 41 and 19 at 97. However, expert testimony, or extrinsic evidence (evidence outside of the claim, specification, and prosecution history) is relied on only when "the claim language remains genuinely ambiguous after consideration of the intrinsic evidence." *Bell & Howard Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1997). Here, after reviewing the intrinsic evidence, it is clear that slide carries its ordinary meaning as a microscope slide and the court construes it as such.

E. The Steps in the Claims Are Not Step-Plus-Function Limitations.

BioGenix argued in their brief that the asserted claims were in step-plus-function format and subject to 35 U.S.C. § 112, ¶6[11] which limits the claimed function by the corresponding step or act in the specification. During the *Markman* hearing, BioGenix did not argue this point, conceding that the argument was weak and not necessary to limit "dispensing" to the "direct dispensing" acts described in the specification.

The language "steps of" in the disputed method claim elements 1[c], 1[d], 1[e], 3[a], 5[e], 5[g], 5[h], 6[a] does not invoke 35 U.S.C. § 112, ¶ 6. In the application of § 112 ¶6 to method claims, the statutory term "steps" refers to "the generic description of elements of a process, and the term "acts" [refers] to the implementation of such steps." *O.I. Corp. v. Tekmar Co. Inc.*, 115 F.3d 1576, 1583 (Fed. Cir. 1997). The statute applies only when the claim recites the steps plus function without reciting the acts supporting the function[12]. *Id.* The tradeoff for using functional expressions without reciting all possible acts in the claim is limiting the claim to the corresponding acts specified in the written description and equivalents thereof. *Id.*

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[11] 35 U.S.C. § 112, ¶ 6:
An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

[12] Step-plus-function applies when:
1) the claim recites **a step** and **a function**; and
2) the claim **does not recite an act** corresponding to the step-plus-function

In addition, in *Cardiac Pacemakers*, the Federal circuit held that § 112 ¶6 should not be applied to a clause which only recites a step in a method claim and does not use the "steps for" language. 381 F.3d 1371, 1382 (Fed. Cir. 2004). The Federal Circuit Court stated, "[m]ethod claims necessarily recite the steps of the method" and the language "the method comprises the steps of" does not change the subsequent claimed steps into step-plus-function form under § 112 ¶6. *Id.* In fact, the absence of "steps for" language creates the presumption that the claimed steps are *not* in step-plus-function form. *Id.* Furthermore, the Federal Circuit Court disregarded the lower court's concern that the claimed steps would be interpreted too broadly without the limitations of § 112 ¶6, stating that "[a] claim limitation is always construed in light of the specification, whatever the form of the claim." *Id.* at 1381.

Given that the asserted claims do not use the "steps for" language and the claimed elements are written as steps in a method claim, or acts, rather than in purely functional terms, the court will not impose step-plus-function limitations in the asserted claims.

CONCLUSION

For the reasons stated in the court's Memorandum on this same date, the disputed claim terms of the '861 patent shall be construed as set forth in the court's Order of this same date.

IT IS HEREBY ORDERED that:

1. The term "**DISPENSING**" is construed to mean "**DIRECT DISPENSING**."
2. The prosecution disclaimer of "**SIP AND SPIT**" dispensing from the parent '052 application attaches to the '861 patent and further **narrows the construction of the term "DISPENSING" by excluding "SIP** AND SPIT DISPENSING" from its meaning.
3. The bar code reader may read the reagent container bar code and the slide bar code in any order.

4. The term "**SLIDE**" is construed to mean "**PLAIN MICROSCOPE SLIDE.**"

5. **STEP-PLUS-FUNCTION** limitations **do not apply** to the asserted claims of the '861 Patent.

Dated this 23rd day of August, 2005.

Raner C. Collins
United States District Judge

Chin, Roger

From: azddb_responses@azd.uscourts.gov
Sent: Monday, August 29, 2005 8:57 AM
To: azddb_nefs@azd.uscourts.gov
Subject: Activity in Case 4:03-cv-00092-RCC Ventana Medical Sys v. Biogenex Labor "Order"

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Case Name: Ventana Medical Sys v. Biogenex Labor
Case Number: 4:03-cv-92
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Document Number: 234

Docket Text:
ORDER: That the term DISPENSING is construed to mean DIRECT DISPENSING. The prosecution disclaimer of SIP AND SPIT dispensing from the parent 052 application attaches to the 861 patent and further narrows the construction of the term DISPENSING by excluding SIP AND SPIT DISPENSING. Signed by Judge Raner C Collins on 8/23/05. (REC,)

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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

- - - - - - - - - - - - - - - - - - x
VENTANA MEDICAL SYSTEMS, INC.,
Plaintiff,
Civil Action
VS No. 05-CV-10614-GAO
VISION BIOSYSTEMS, INC.,
Defendant.
- - - - - - - - - - - - - - - - - - x

AUDIOVISUAL DEPOSITION OF ROSS BARROW, a witness called by counsel for the Plaintiff, taken pursuant to the Federal Rules of Civil Procedure, before Helana Eve Kline, a Massachusetts Certified Shorthand Reporter & Registered Professional Reporter and Notary Public in and for the Commonwealth of Massachusetts, at the Offices of Vision Biosystems, Inc., 700 Longwater Drive, Norwell, Massachusetts, on Tuesday, September 6, 2005, commencing at 9:25 a.m.

ROTHWELL, FIGG, ERNST & MANBECK, P.C.

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October 6, 2005

Via Facsimile

Ron E. Shulman, Esq..
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, CA 94304

Re: Vision BioSystems (USA) Trading, Inc. v. Ventana Medical Systems, Inc.
District of Mass. 03 CV 10391 GAO
Ventana Medical Systems, Inc. v. Vision BioSystems Inc.
District of Mass. 05-CV-10614-GAO
Our Refs.: 2961-101 and 2961-102

Dear Ron,

Confirming the voice-mail message that I left for you earlier today, we just received word that the Arizona court has entered a final, appealable judgment of noninfringement in the Ventana v. Biogenix litigation. It is Vision's intention to file a motion for summary judgment of noninfringement in the above-referenced cases based on collateral estoppel and issue preclusion.

I would like to speak with you about this motion to discuss whether Ventana will consent to the entry of judgment, without prejudice to Ventana's contesting on appeal the underlying bases for the Arizona court's judgment. I also would like to speak with you concerning the impact that the Arizona court's judgment has on the current schedules in the Massachusetts cases.

I will be leaving the office at about 4:00 pm my time today. If you cannot reach me, please speak with Elizabeth Leff.

ROTHWELL, FIGG, ERNST & MANBECK, P.C.

In view of your intention to expedite the appeal in the Federal Circuit, we would like to get resolution of this matter before Judge O'Toole as soon as possible. We intend to file the Vision motion early afternoon tomorrow (EST); therefore, we request that you return my call before then.

Very truly yours,

E. Anthony Figg

EAF:jmp

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DATE: October 6, 2005

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OUR REF: 2961-102

Number of Pages Including This Transmittal Sheet: 3

If any problems in connection with this facsimile, please contact: Wendy at 202-783-6040.

US006352861B1

(12) **United States Patent**
Copeland et al.

(10) **Patent No.: US 6,352,861 B1**
(45) **Date of Patent: Mar. 5, 2002**

(54) **AUTOMATED BIOLOGICAL REACTION APPARATUS**

(75) Inventors: **Keith G. Copeland**; **Thomas M. Grogan**; **Charles Hassen**; **William Ross Humphreys**; **Charles E. Lemme**; **Phillip C. Miller**; **William L. Richards**; **Wayne A. Showalter**, all of Tucson, AZ (US)

(73) Assignee: **Ventana Medical Systems, Inc.**, Tucson, AZ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/452,309**

(22) Filed: **Dec. 1, 1999**

Related U.S. Application Data

(63) Continuation of application No. 08/906,678, filed on Aug. 5, 1997, which is a continuation of application No. 08/479,415, filed on Jun. 6, 1995, now Pat. No. 5,654,200, which is a division of application No. 08/352,966, filed on Dec. 9, 1994, now Pat. No. 5,595,707, which is a continuation of application No. 07/924,052, filed on Aug. 31, 1992, now abandoned, which is a continuation-in-part of application No. 07/488,601, filed on Mar. 2, 1990, now abandoned.

(51) **Int. Cl.**[7] **G01N 1/00**; G01N 35/04

(52) **U.S. Cl.** **436/46**; 436/43; 436/45; 436/47; 436/49; 436/54; 436/180; 422/63; 422/64; 422/65; 422/67; 422/100; 422/102; 427/2.11; 141/130; 141/145

(58) **Field of Search** 422/63–65, 100, 422/67, 102; 436/43, 45, 46, 47, 49, 54, 180; 427/2.11; 141/130, 145

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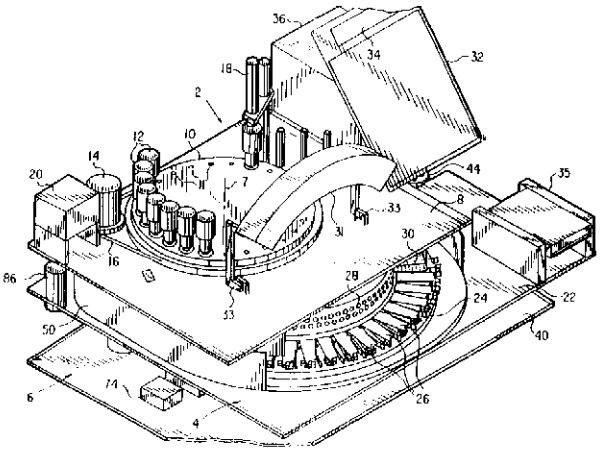
Primary Examiner—Jill Warden
Assistant Examiner—Kathryn Bex
(74) *Attorney, Agent, or Firm*—McDonnell Boehnen Hulbert & Berghoff

(57) **ABSTRACT**

An automated immunostaining apparatus having a reagent application zone and a reagent supply zone. The apparatus has a carousel slide support supporting a plurality of slide supports thereon, and drive means engaging the carousel slide support for consecutively positioning each of a plurality of slide supports in the reagent application zone. The apparatus also has a carousel reagent support having a plurality of reagent container supports thereon, and drive means engaging the carousel for rotating the carousel and positioning a preselected reagent container support in the reagent supply zone. The apparatus also has a reagent delivery actuator means positioned for engaging a reagent container positioned on a container support in the reagent delivery zone and initiating reagent delivery from the reagent container to a slide supported on a slide support in the reagent receiving zone.

25 Claims, 37 Drawing Sheets



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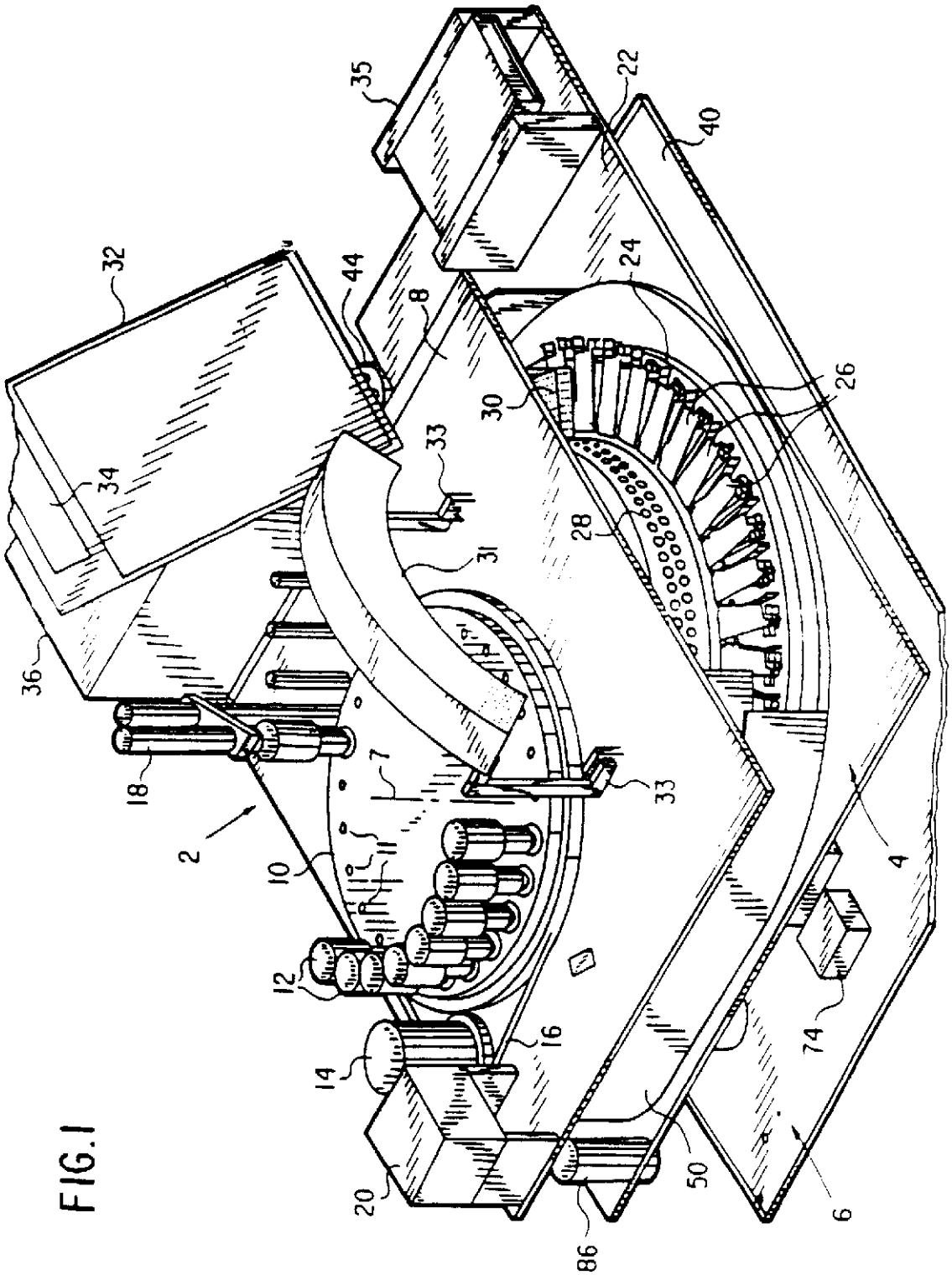
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FIG. 1

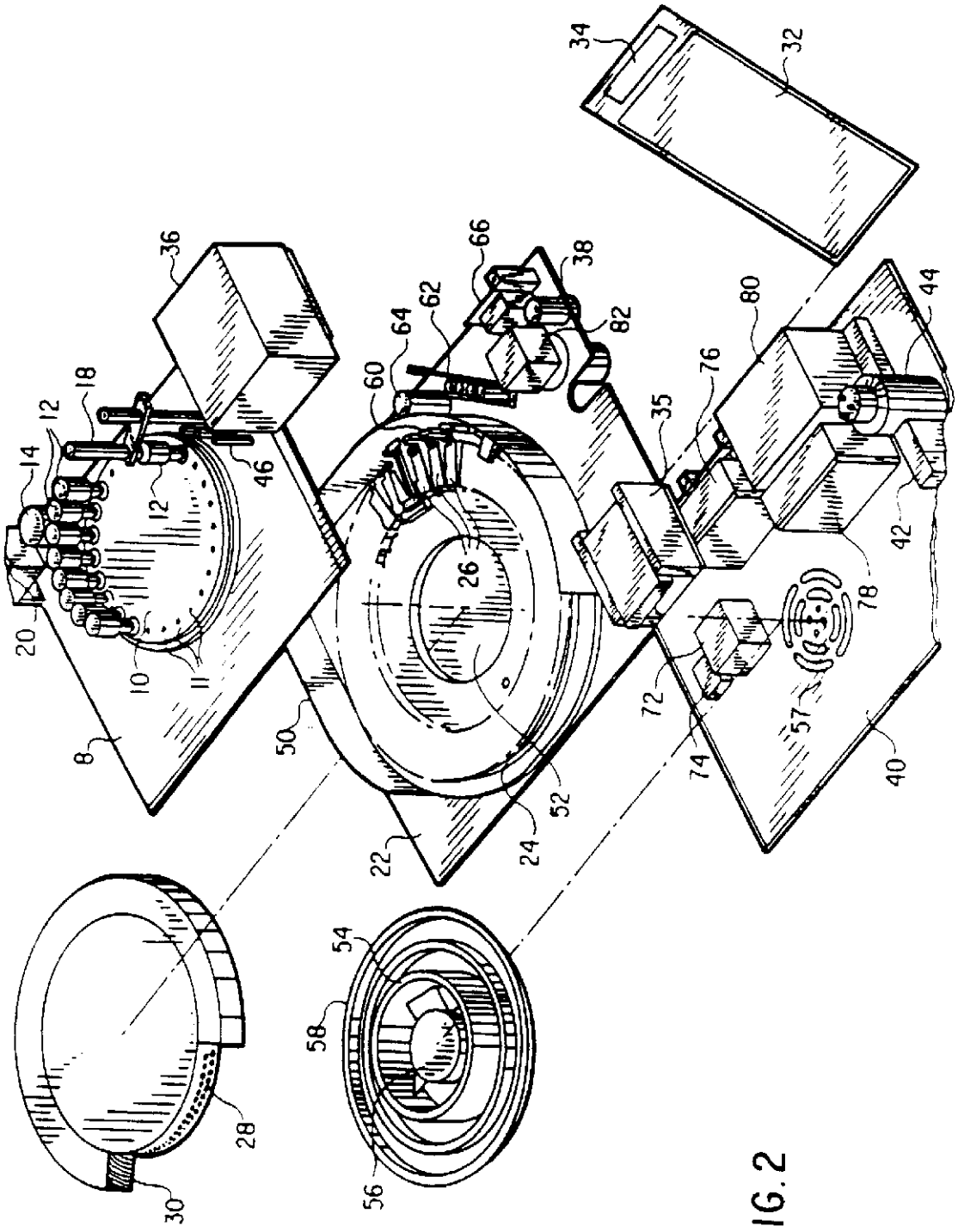
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FIG. 2

FIG.3

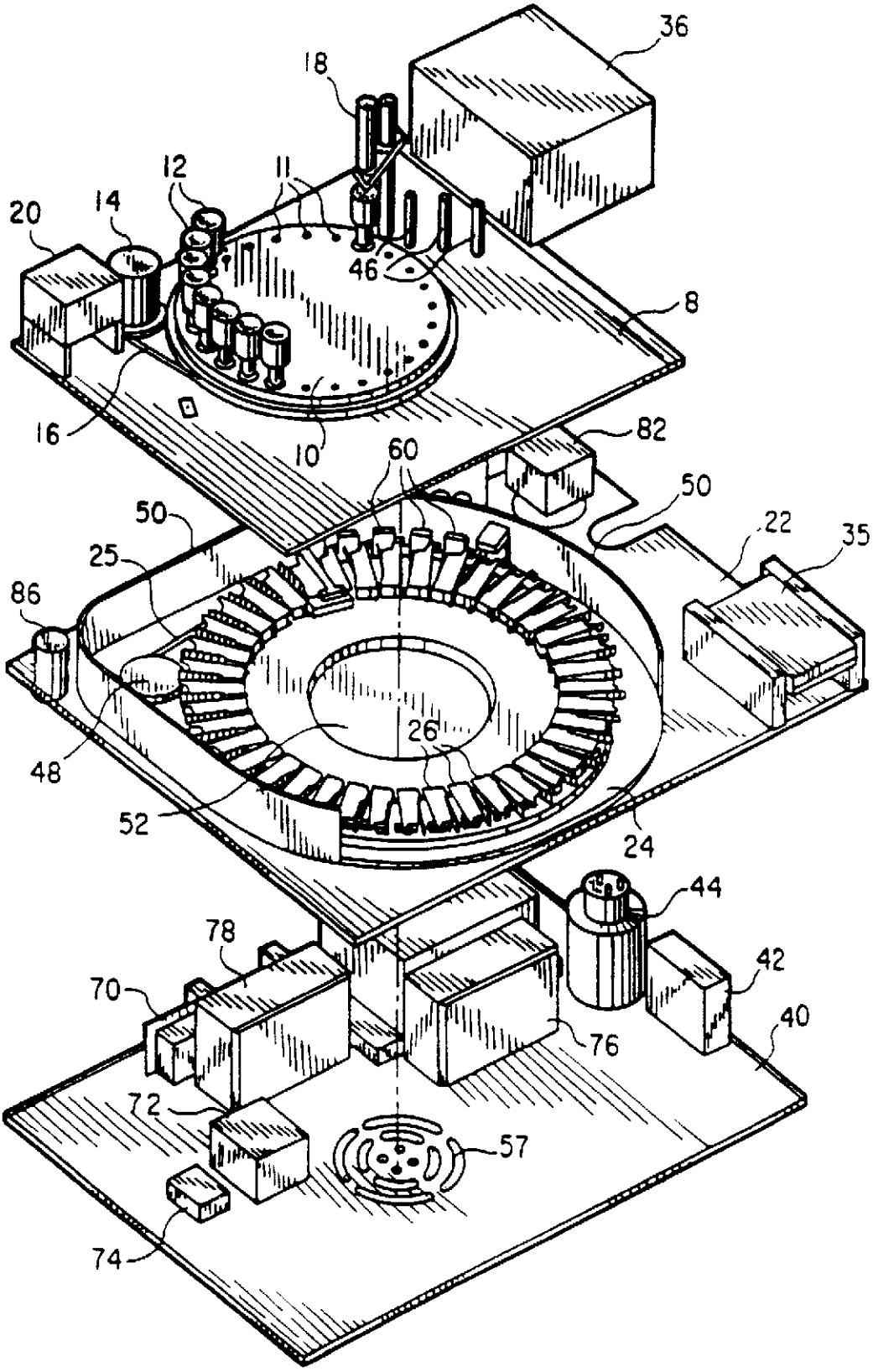
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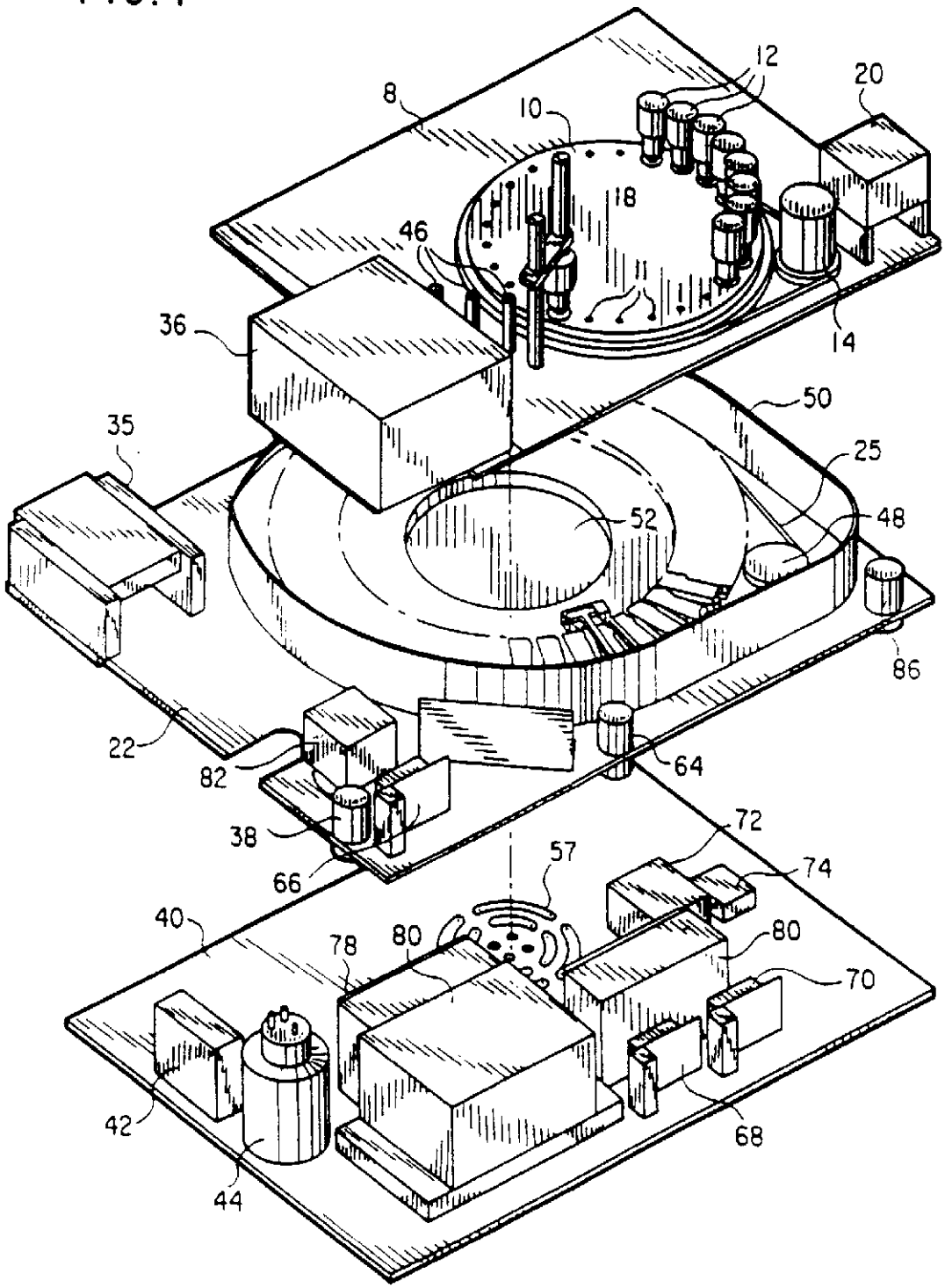
FIG.4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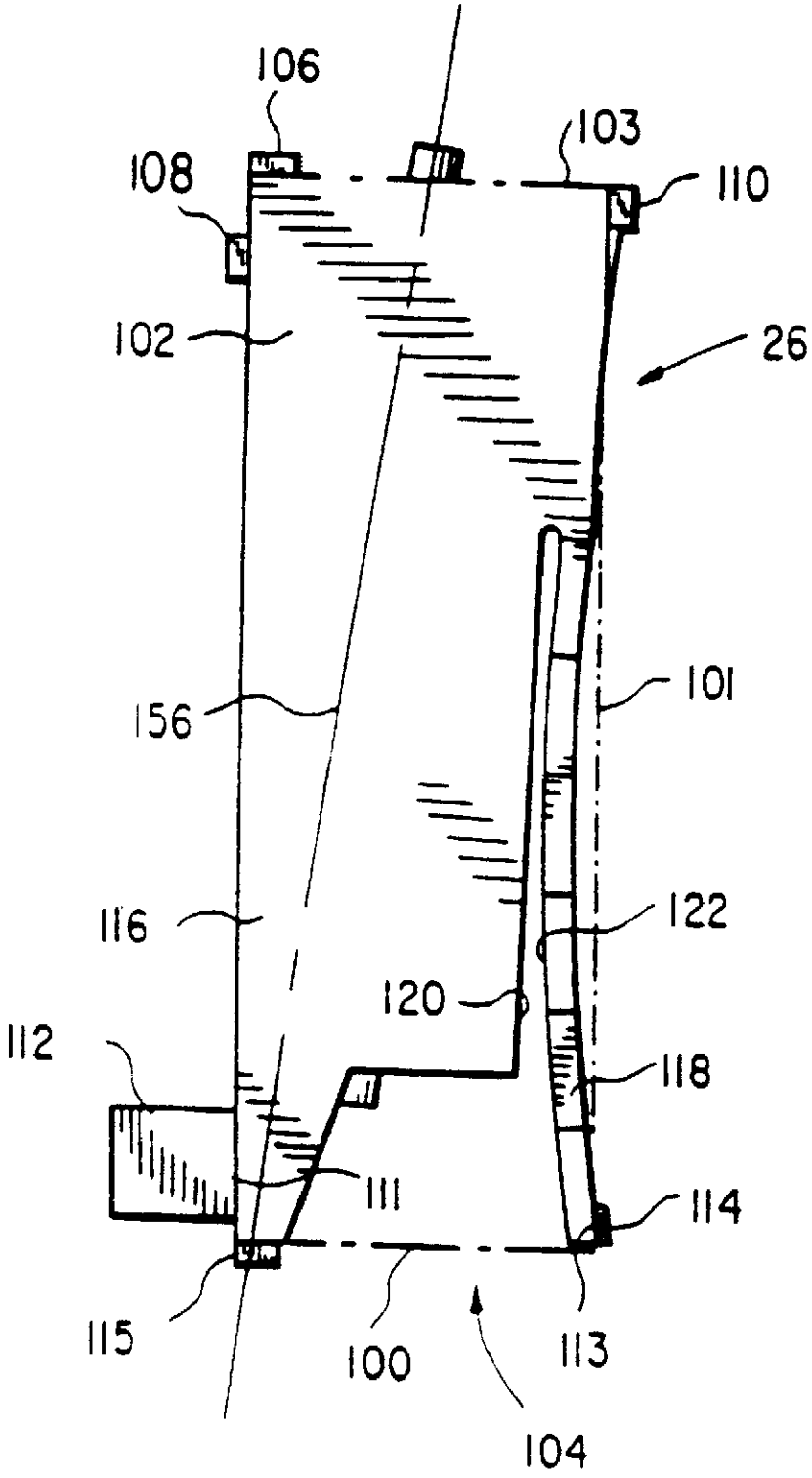
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FIG. 5

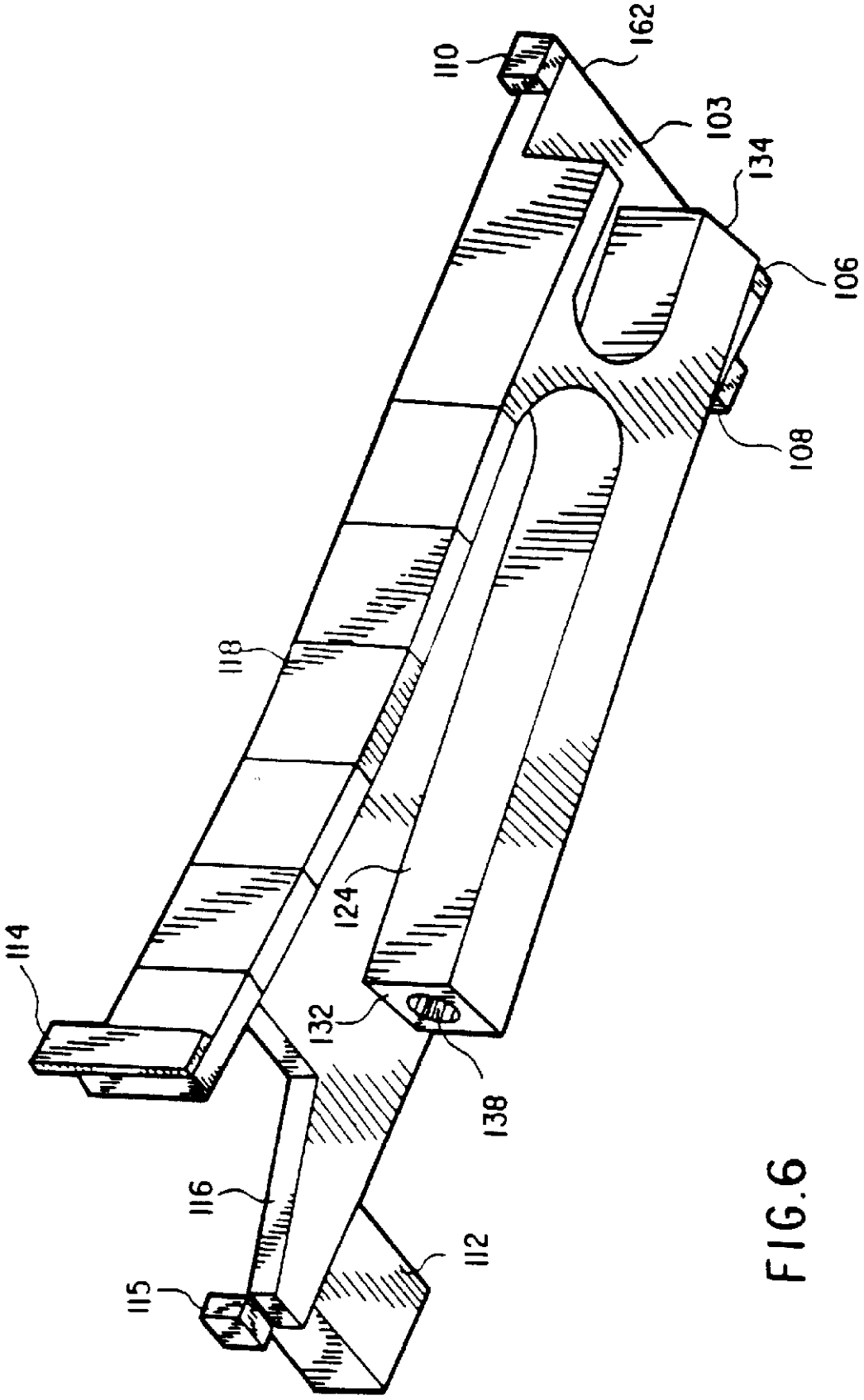
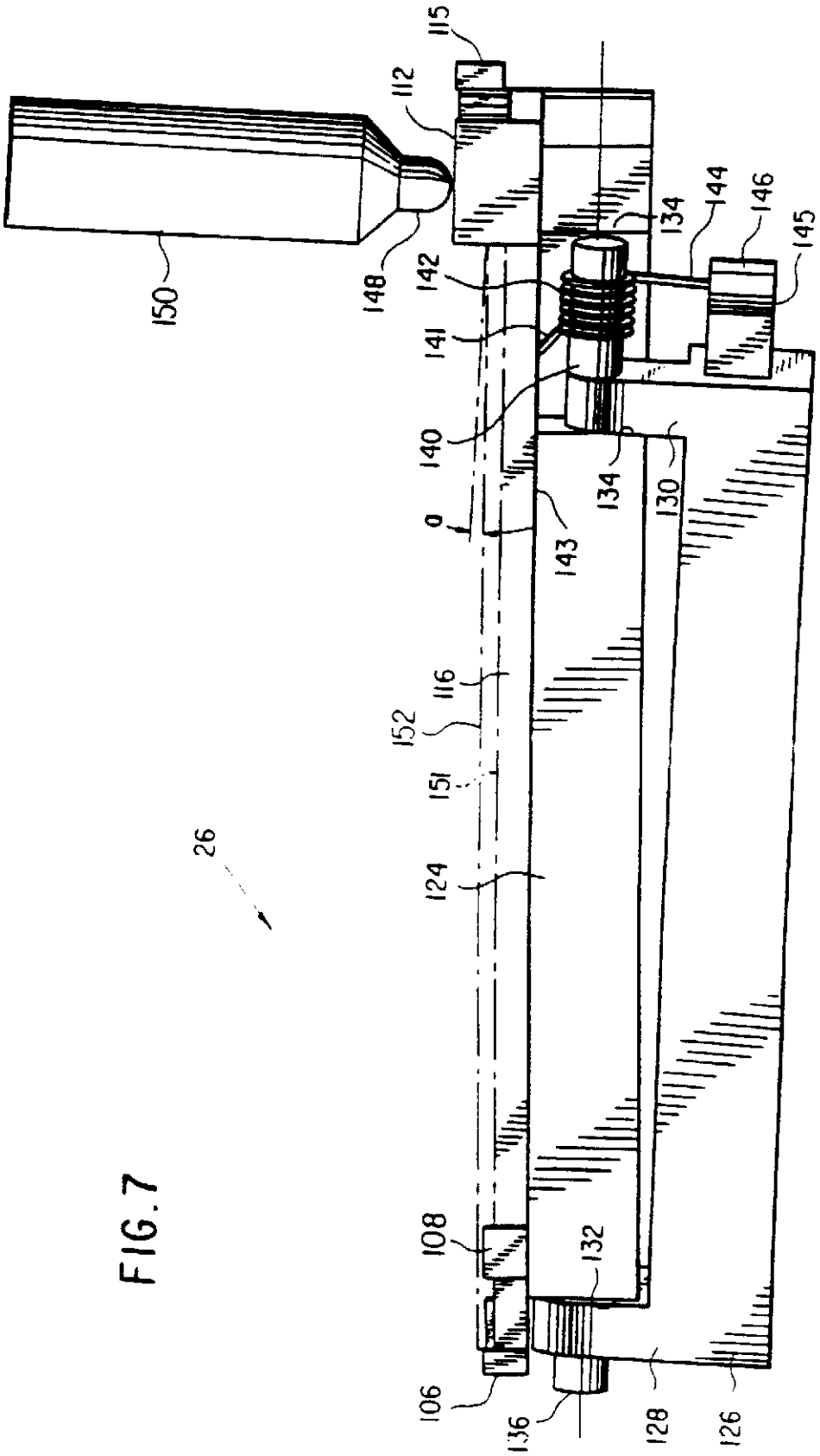


FIG.6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108
132
106
136
128
126

FIG. 7

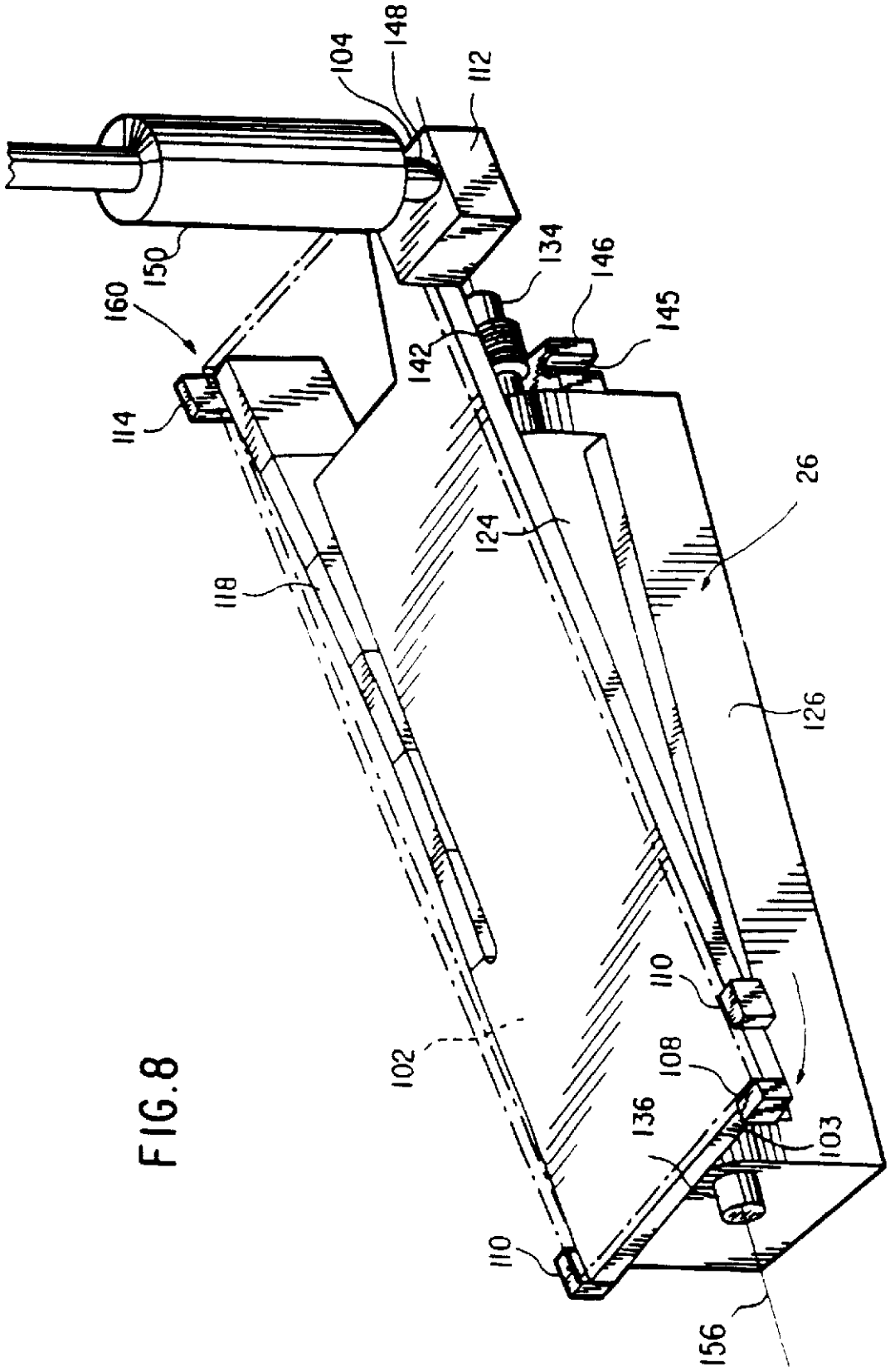
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FIG. 8

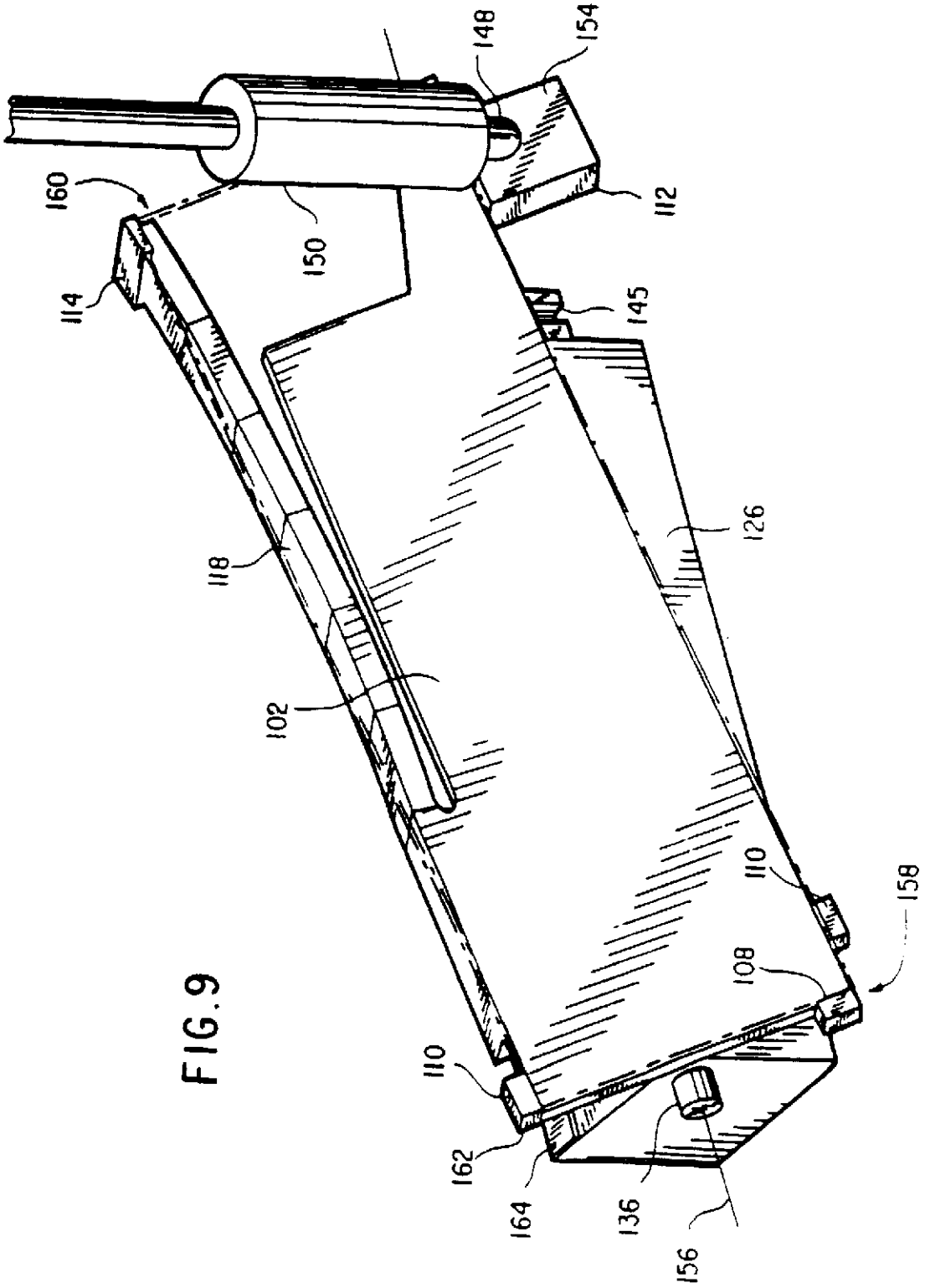
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FIG. 9

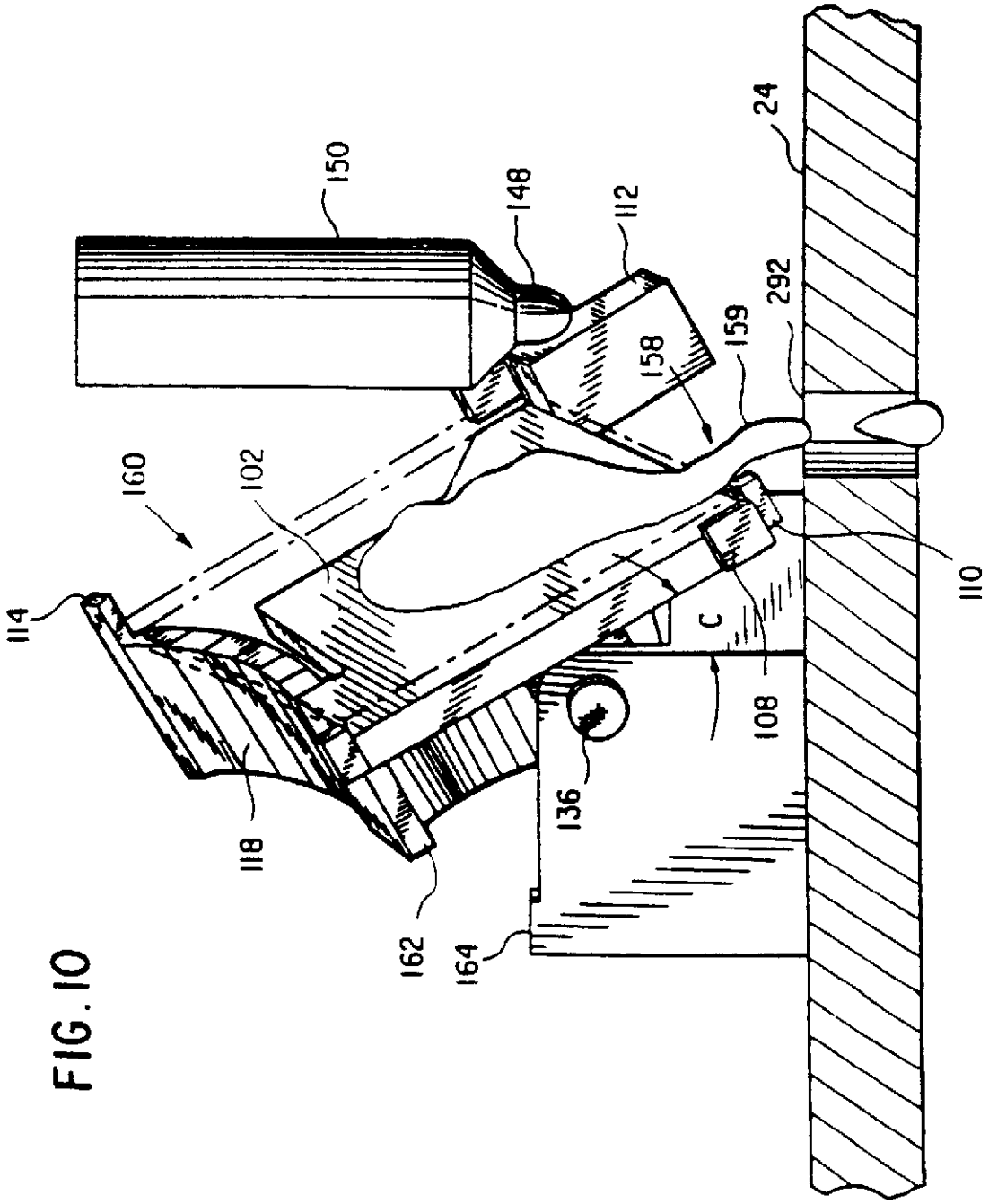
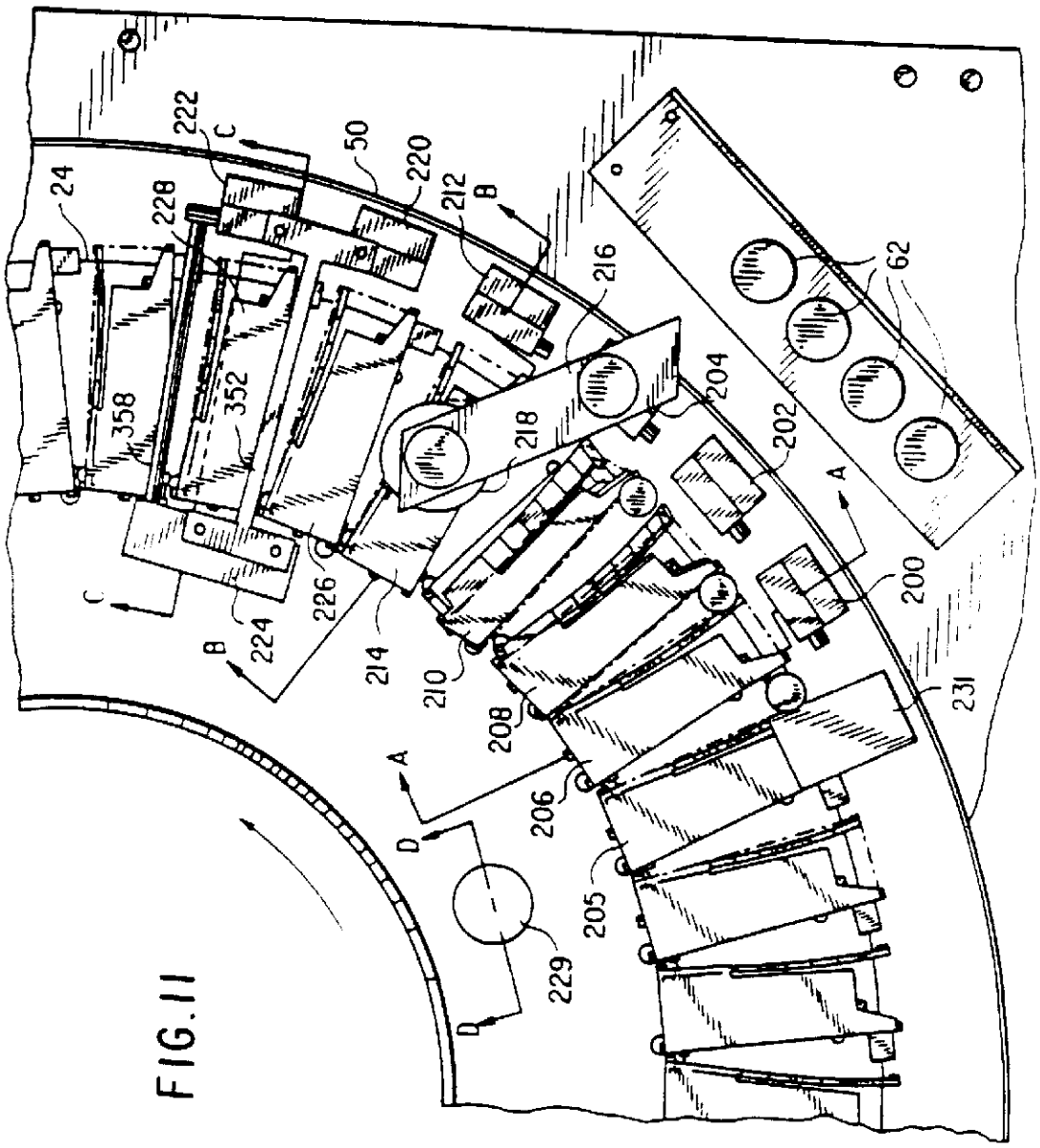


FIG. 10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231
A
206
D
205
229
D

FIG. 11

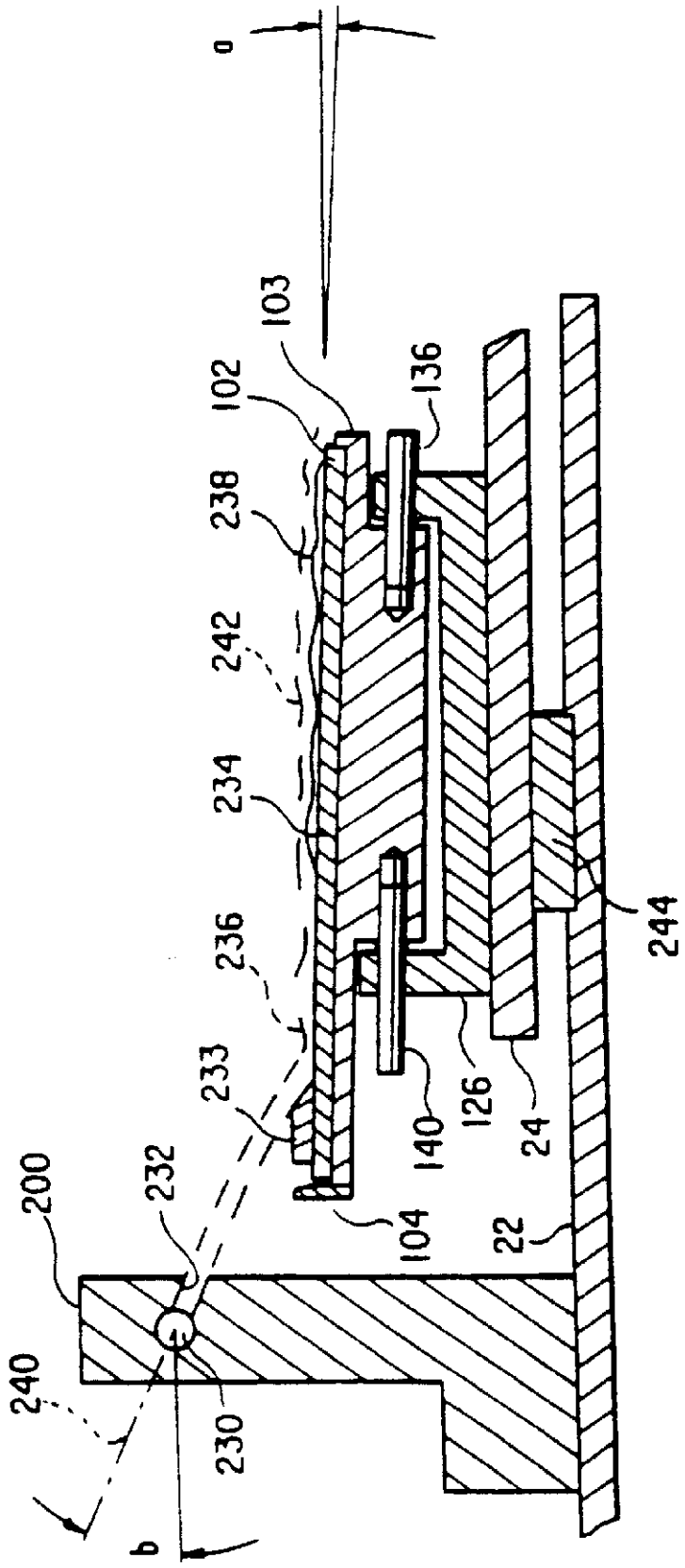
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FIG. 12

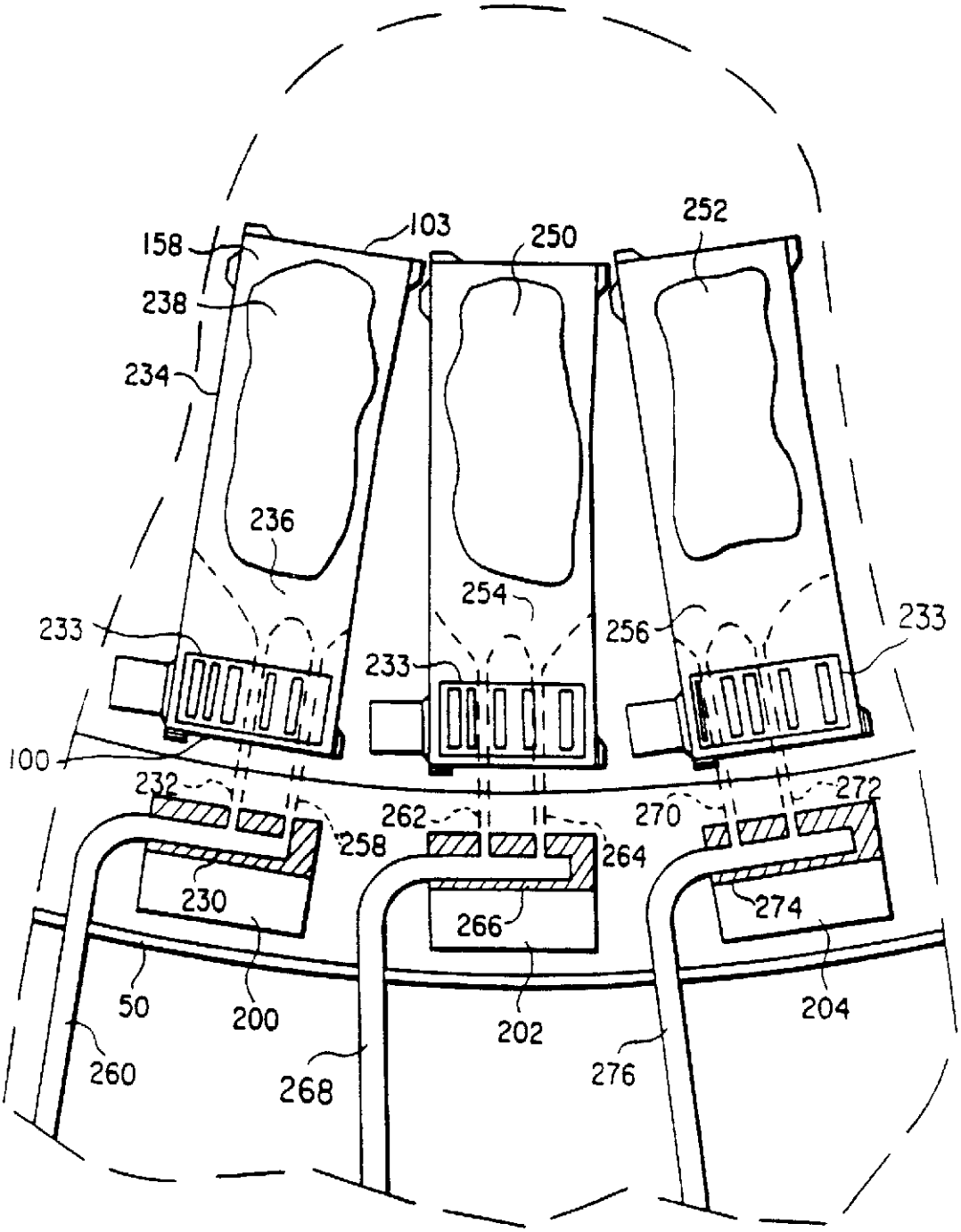
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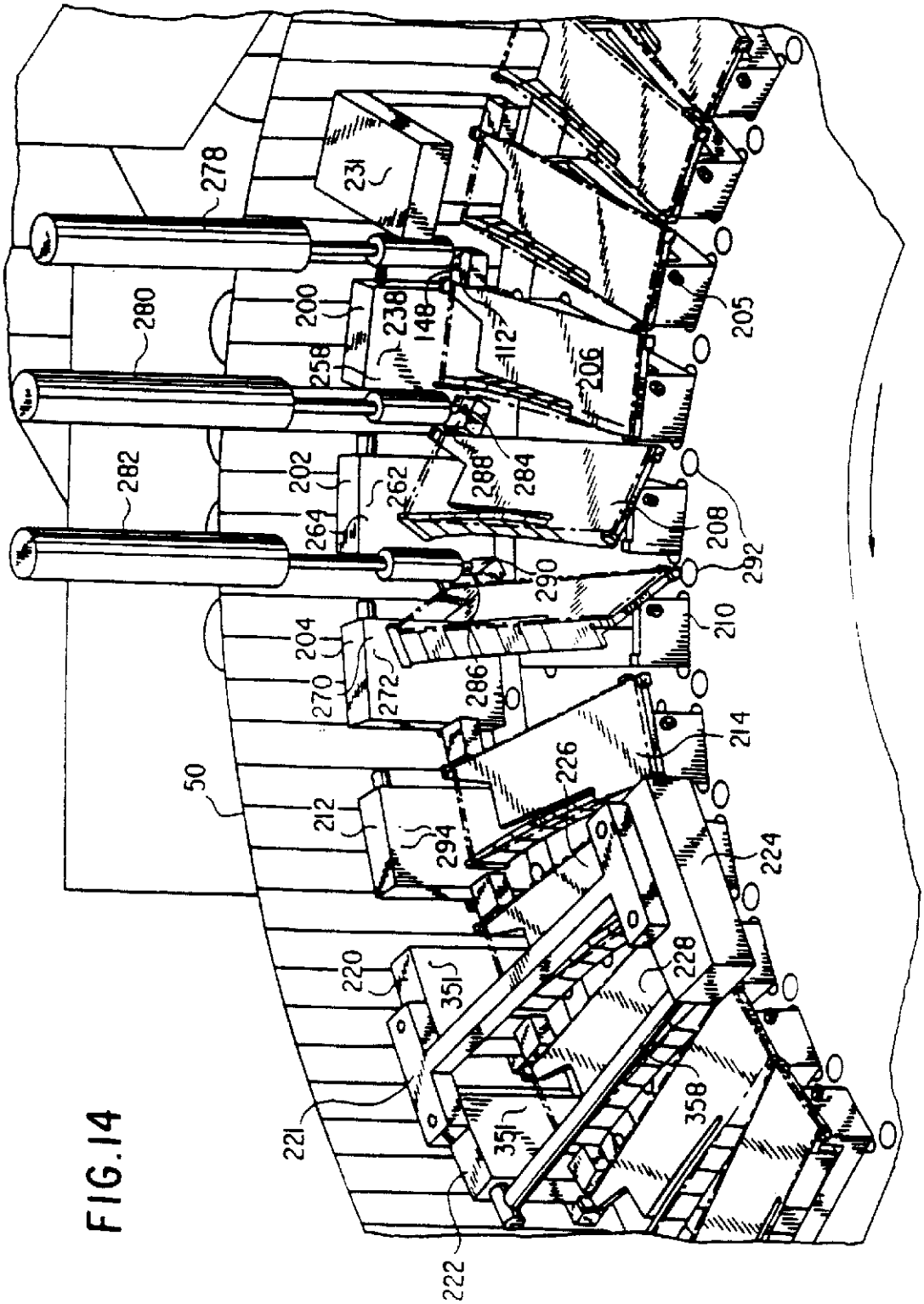
FIG.13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222

FIG. 14

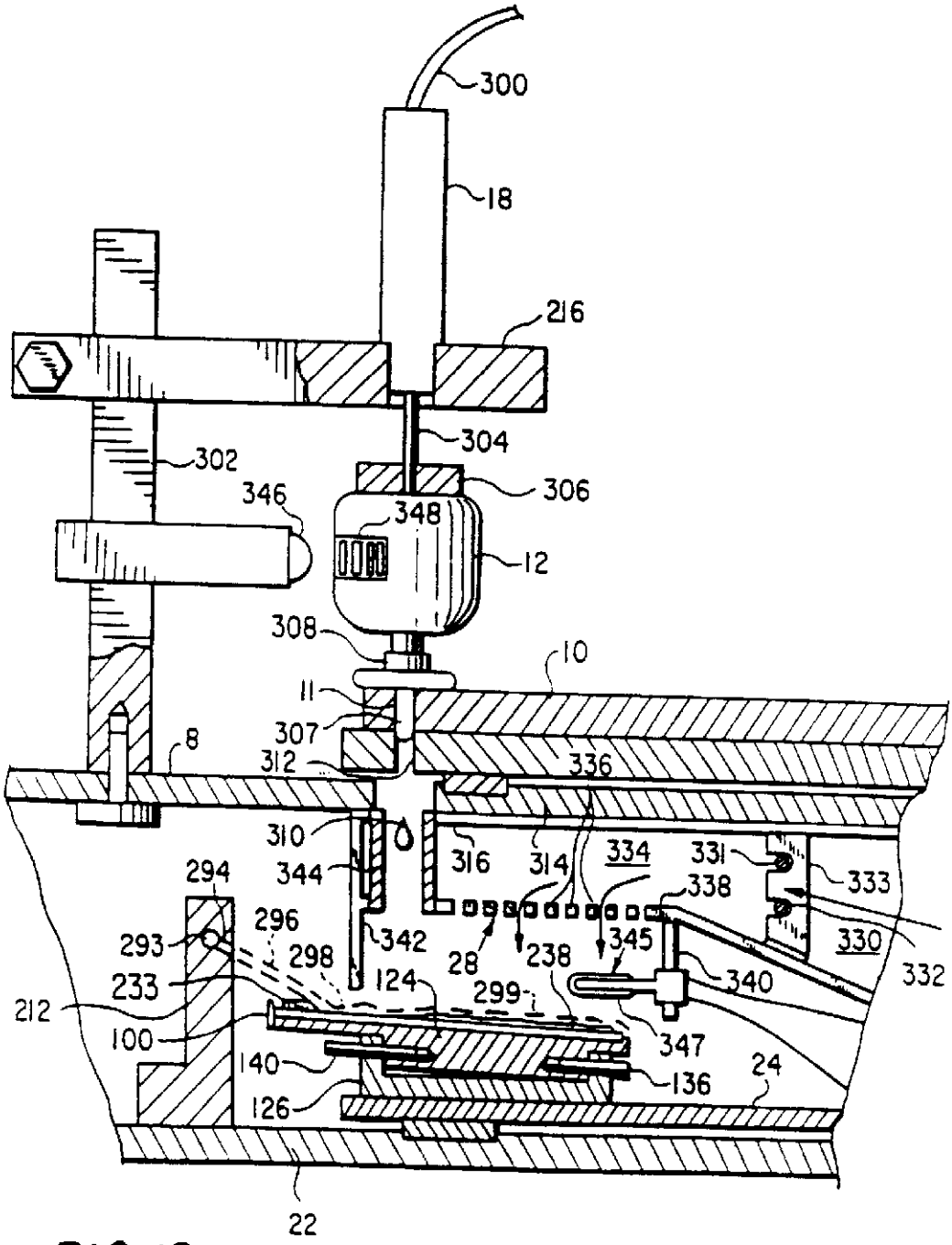
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FIG. 15

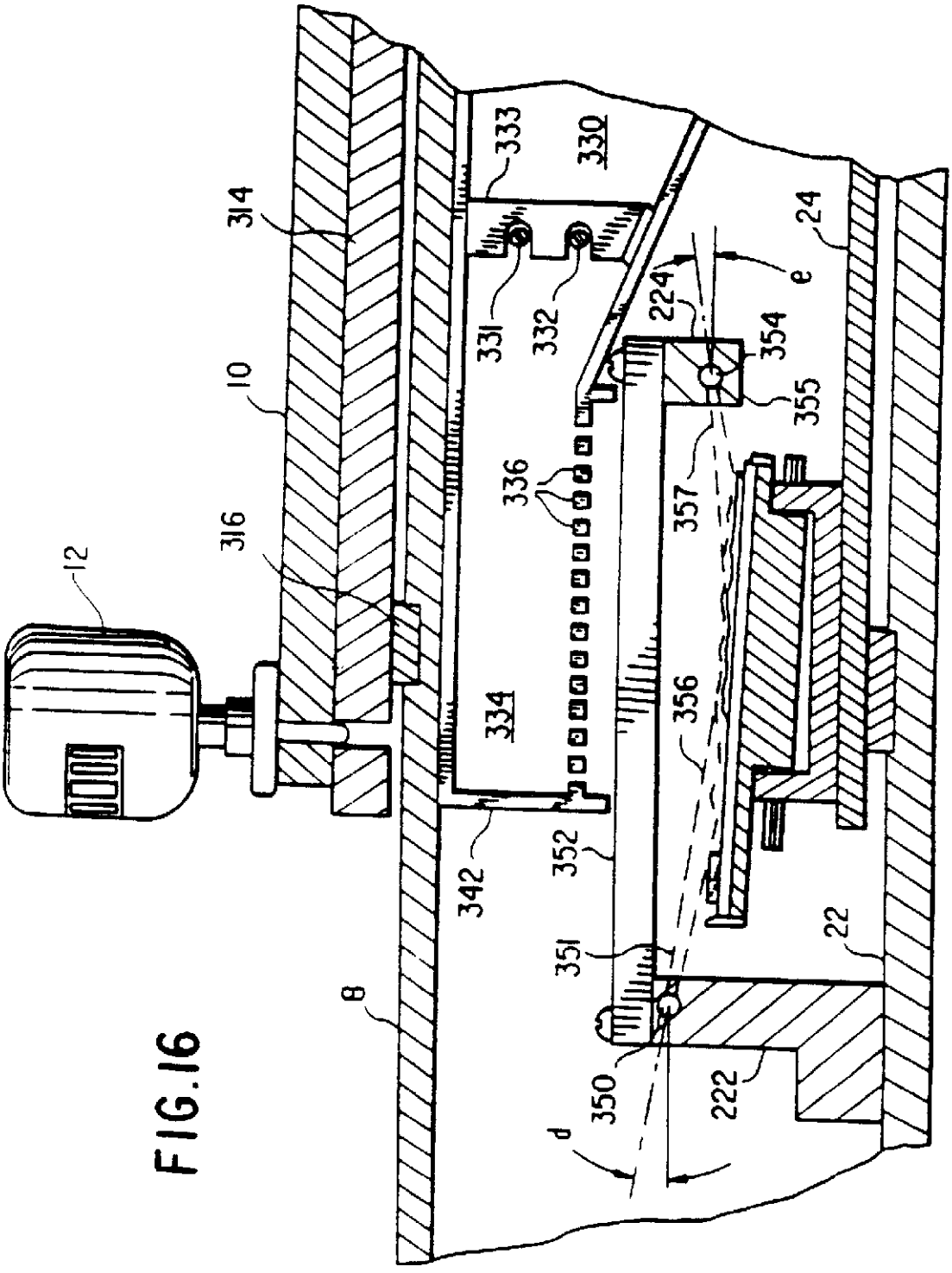
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FIG.16

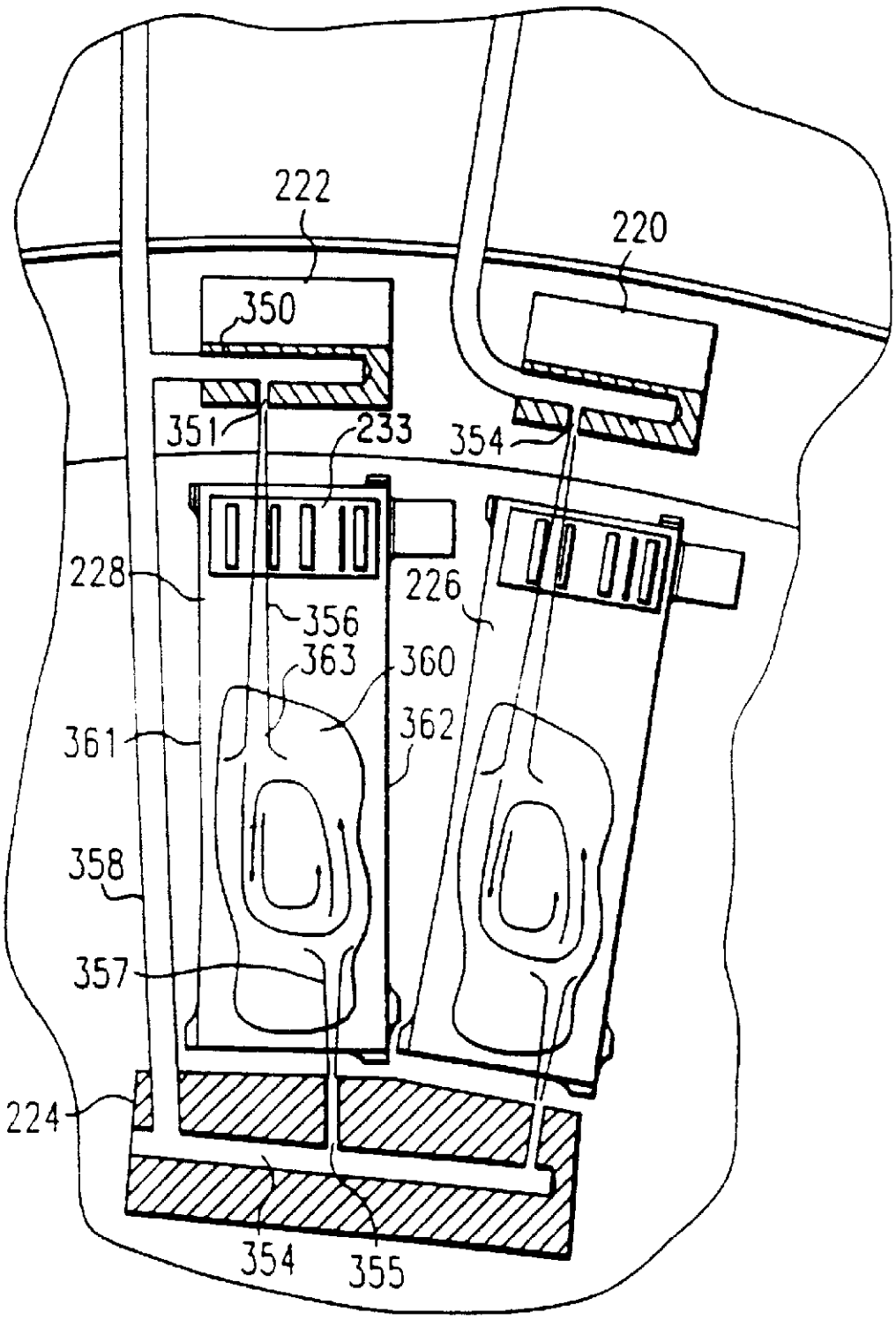
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FIG. 17

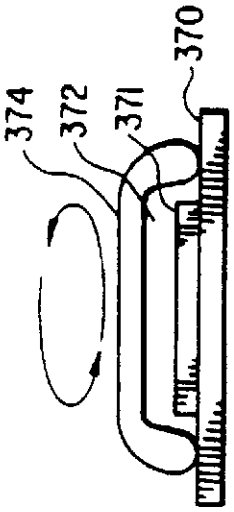

FIG. 18C

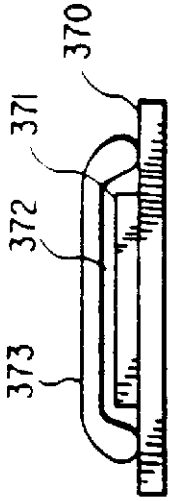

FIG. 18B

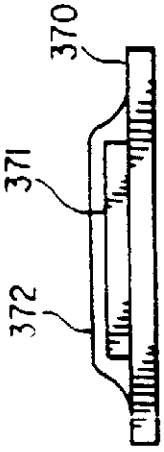

FIG. 18A

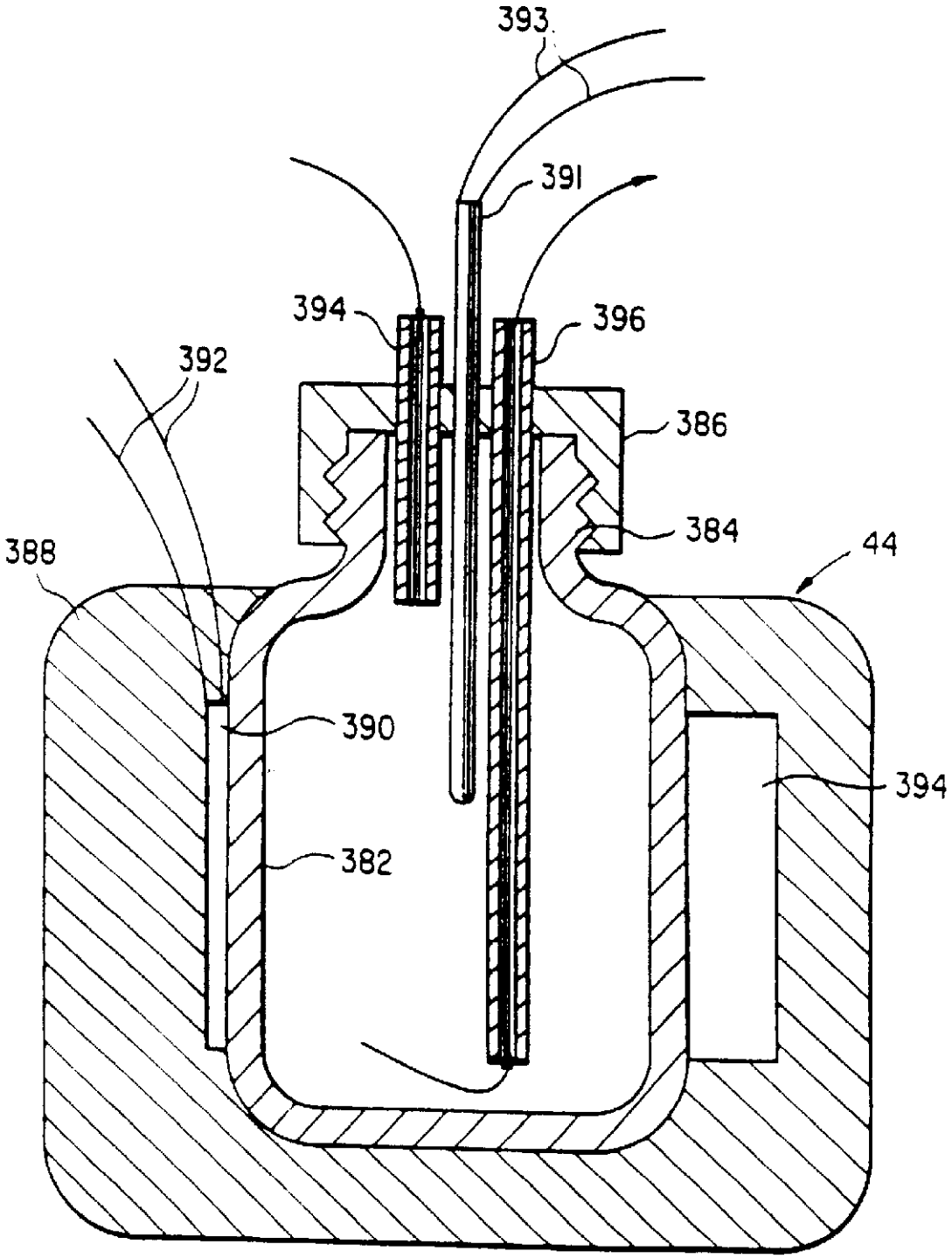

FIG. 19A

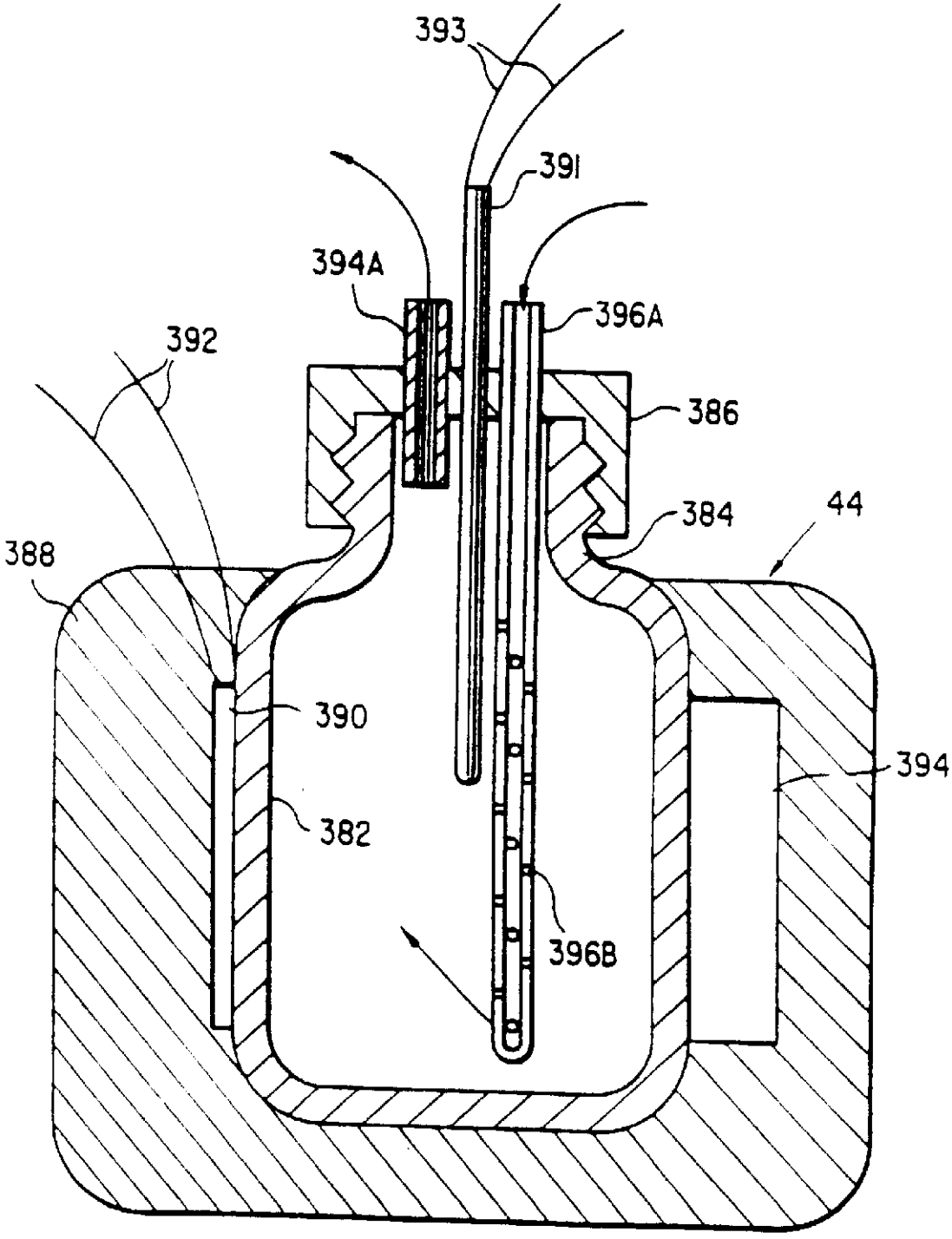

FIG.19B

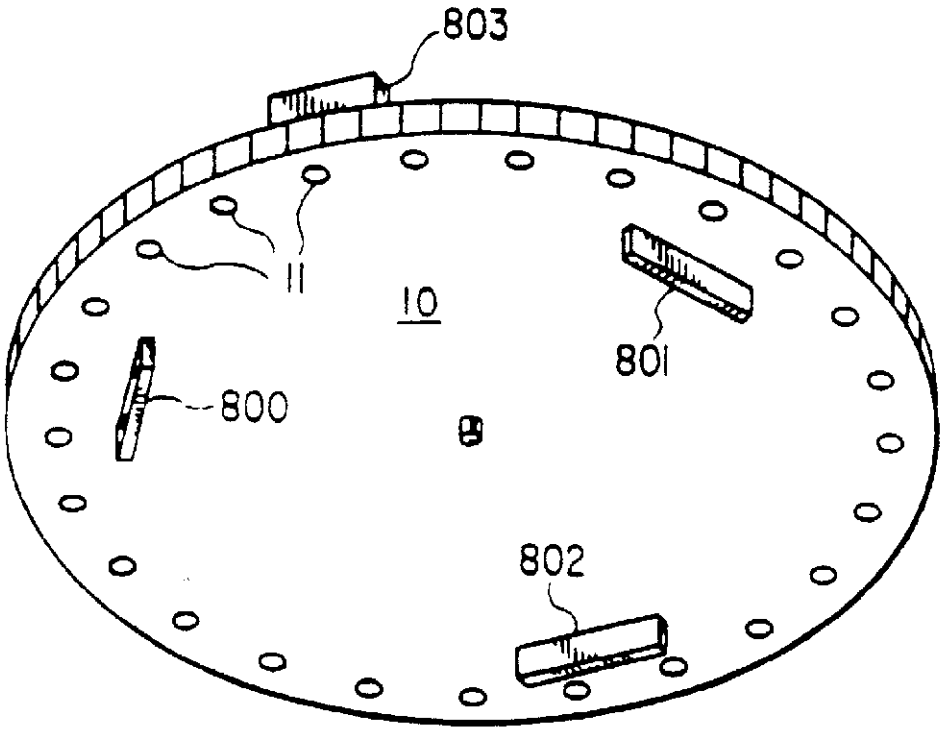

FIG. 20A

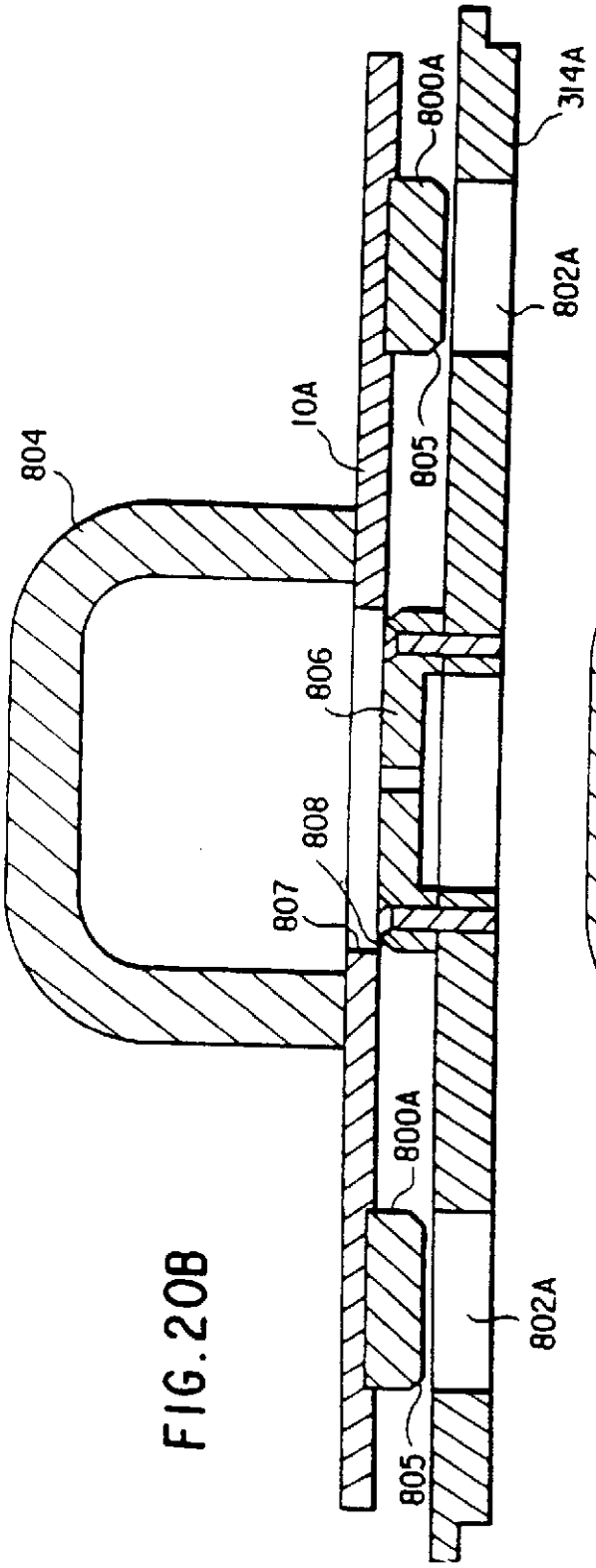

FIG. 20B

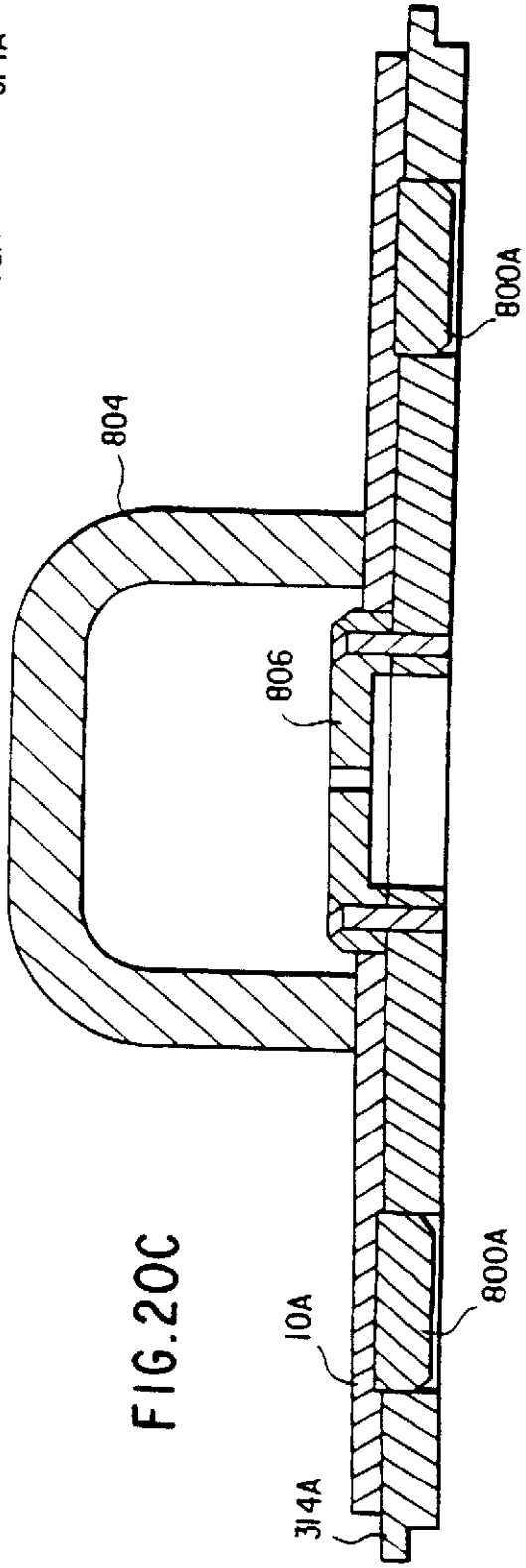

FIG. 20C

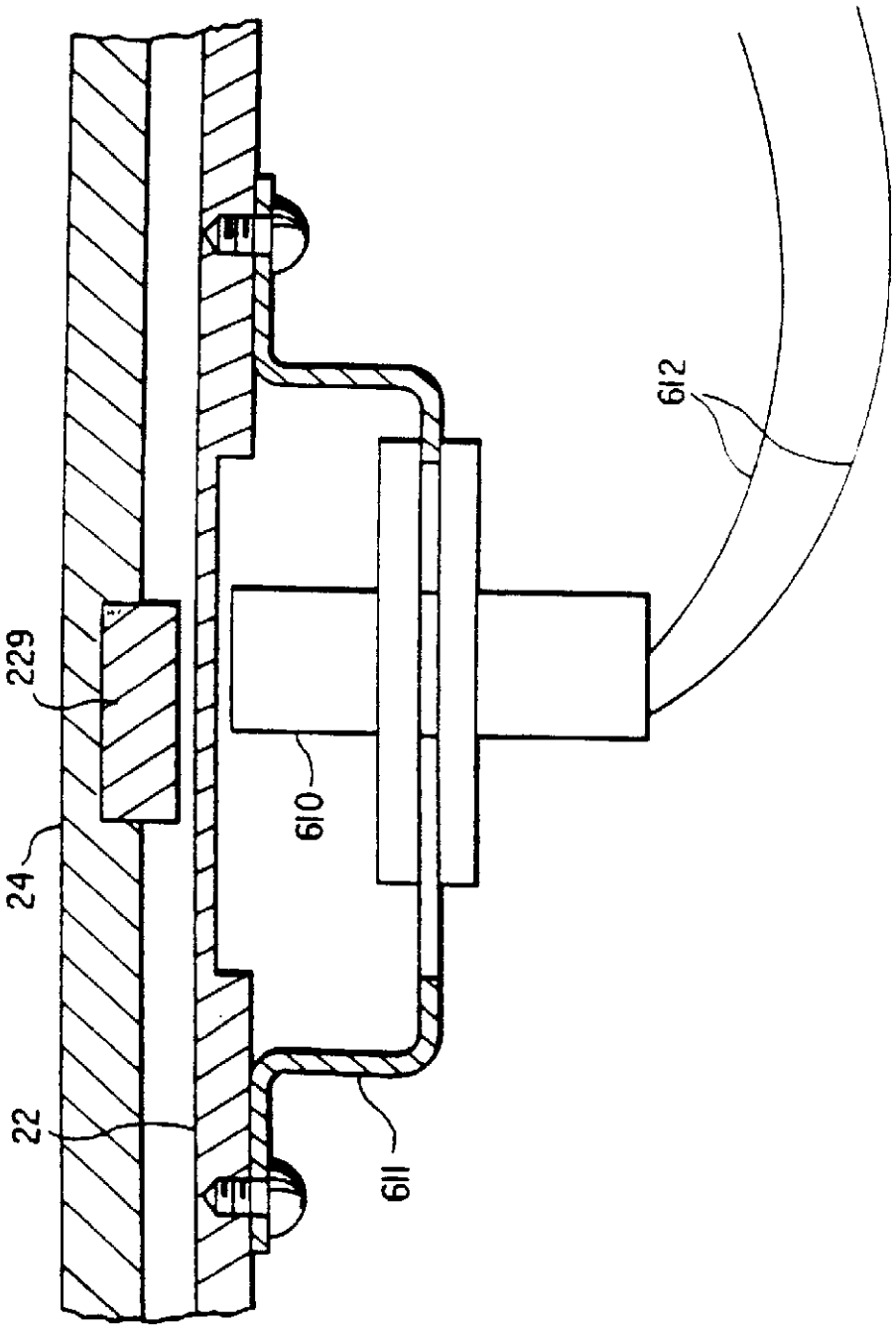

FIG. 21

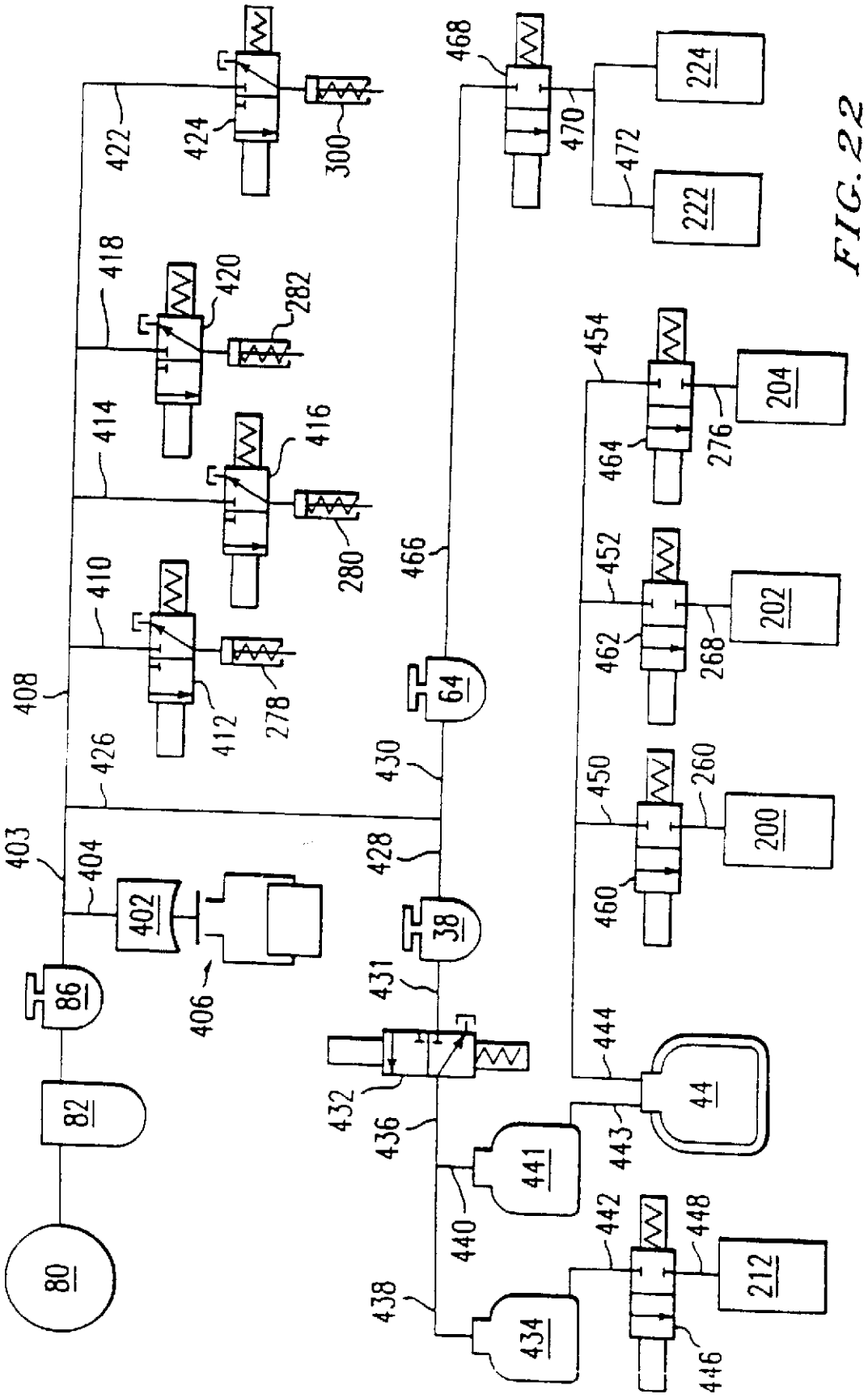
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FIG. 22

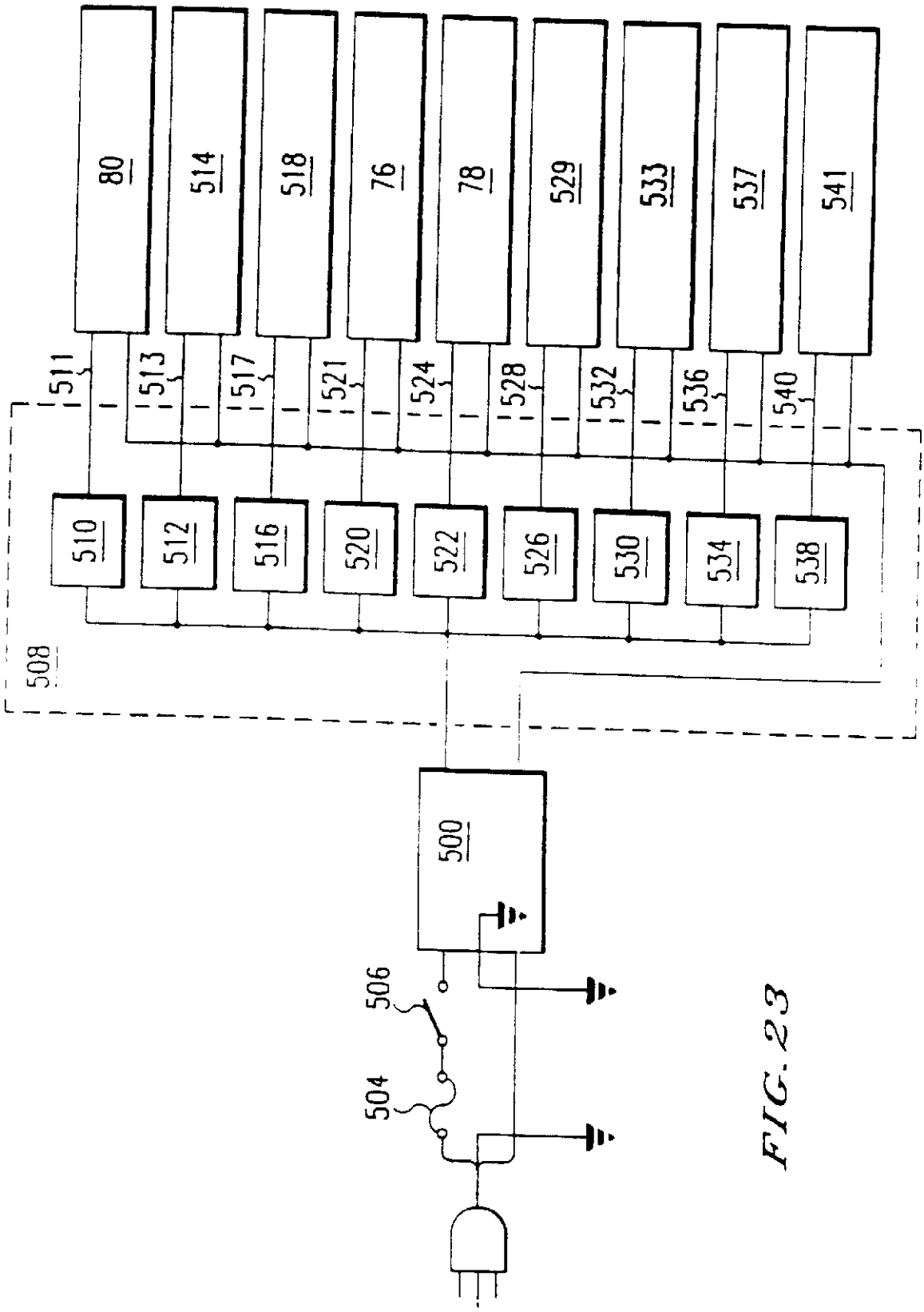
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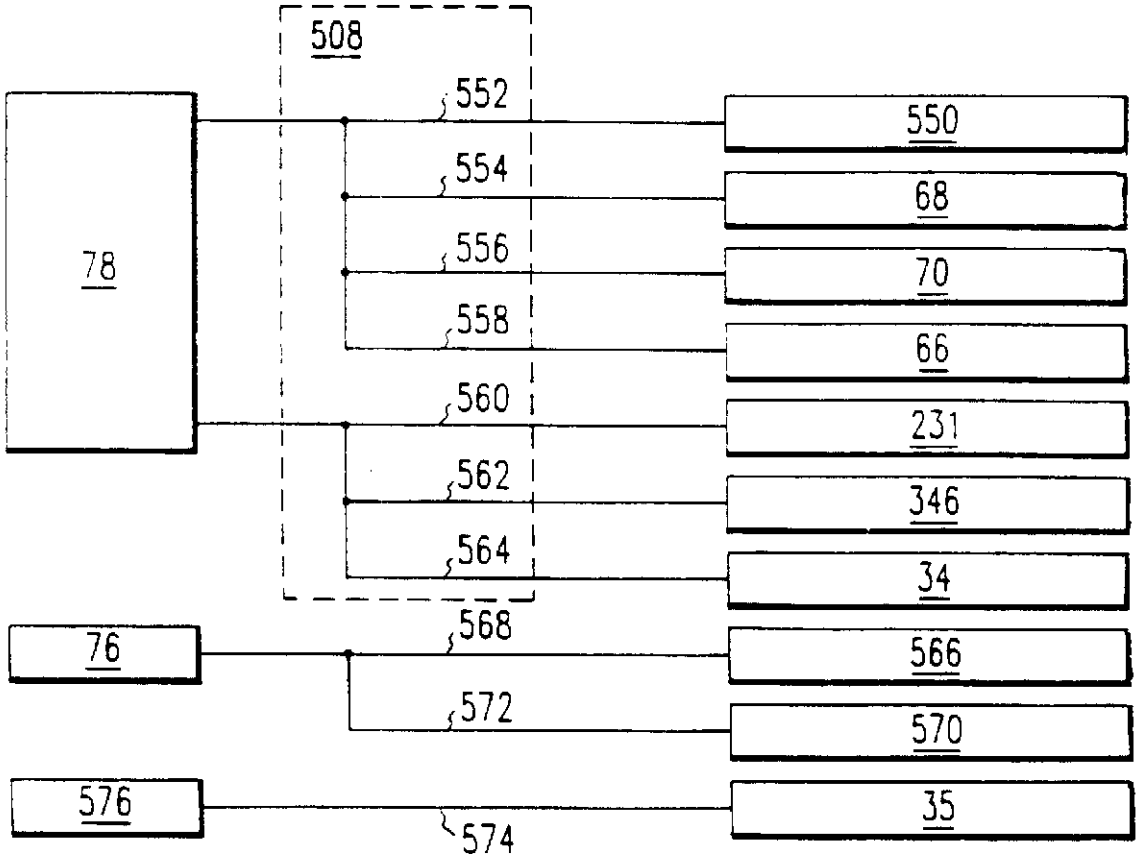
FIG. 23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570
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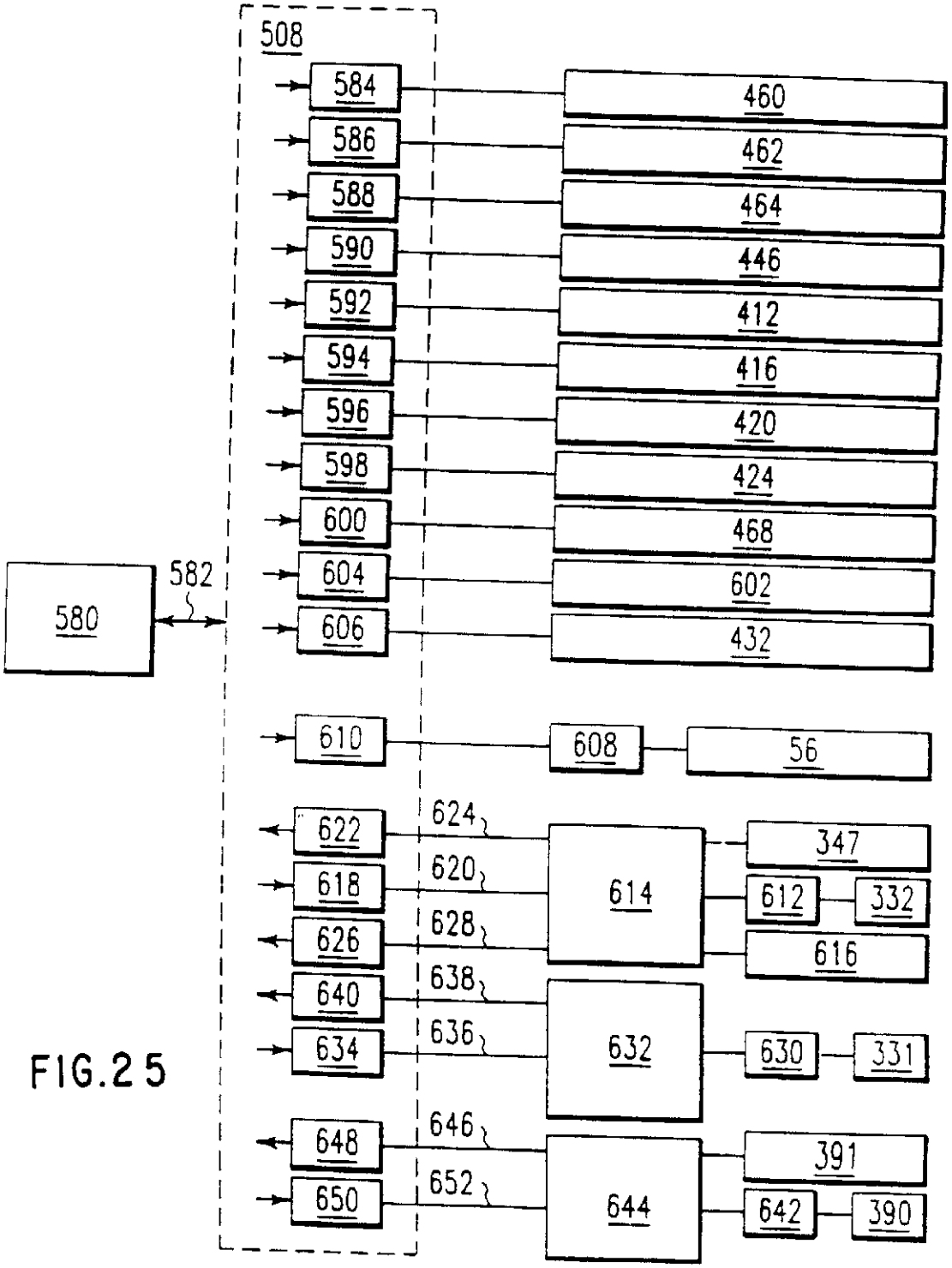
FIG. 24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432
580
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608
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622
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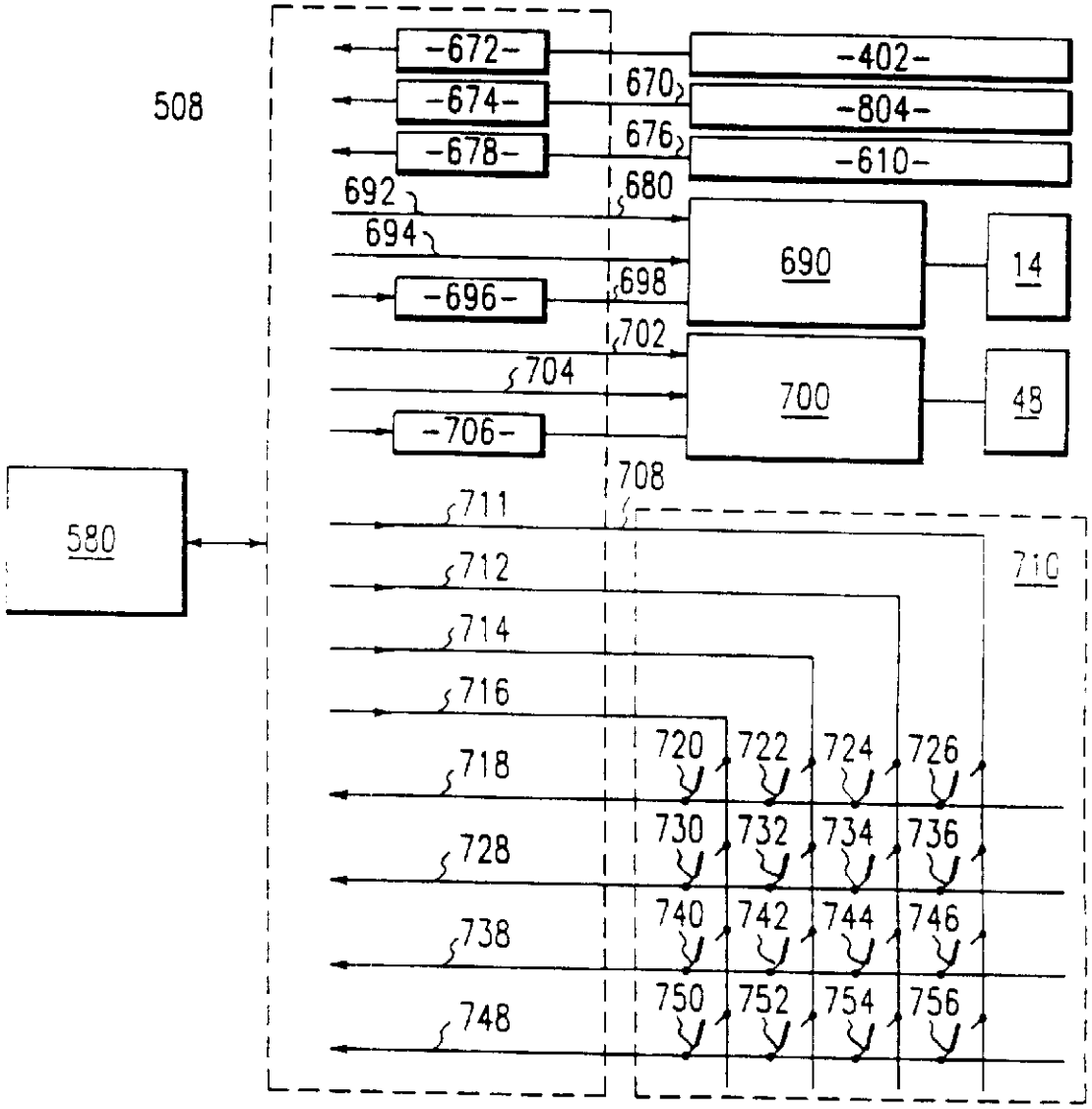
391
642
390

FIG.25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670
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-706-
-402-
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738
748
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744
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754
756

FIG. 26

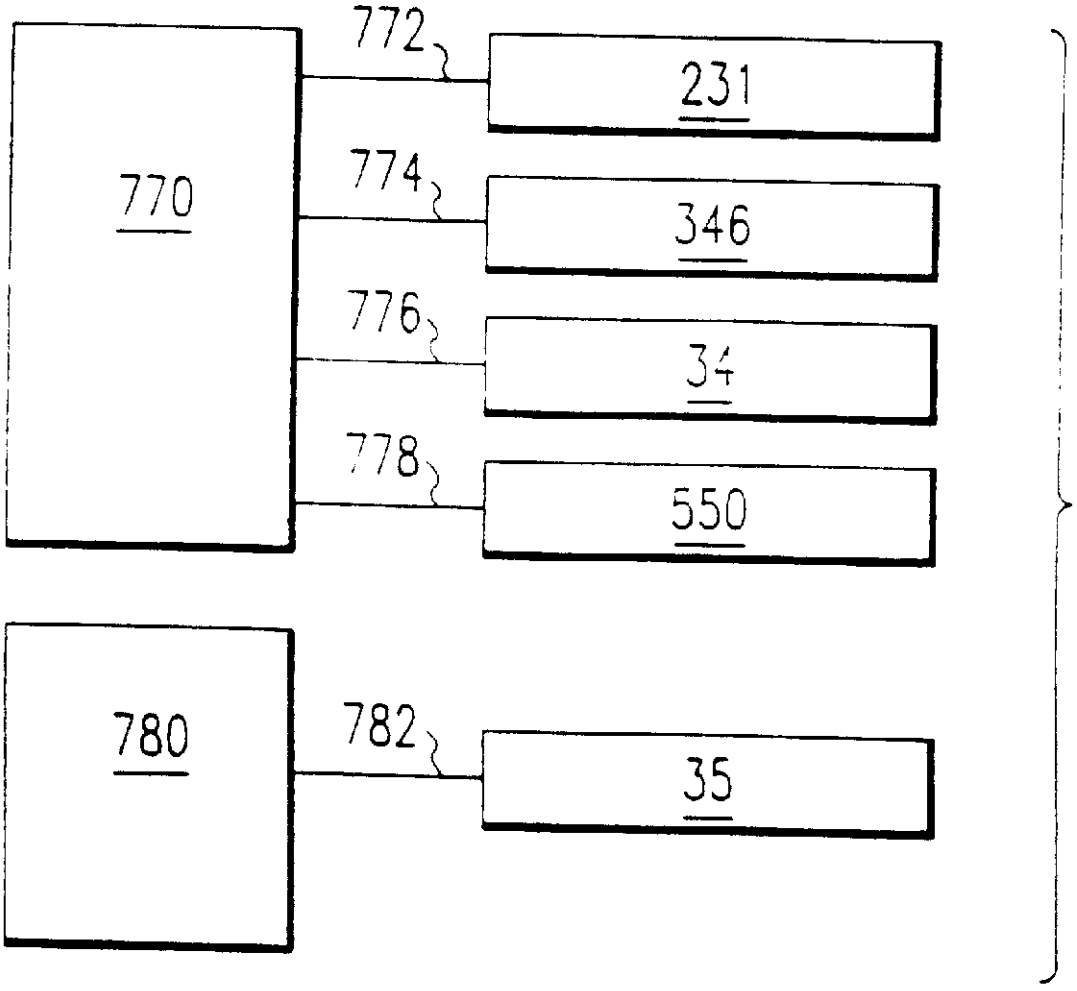
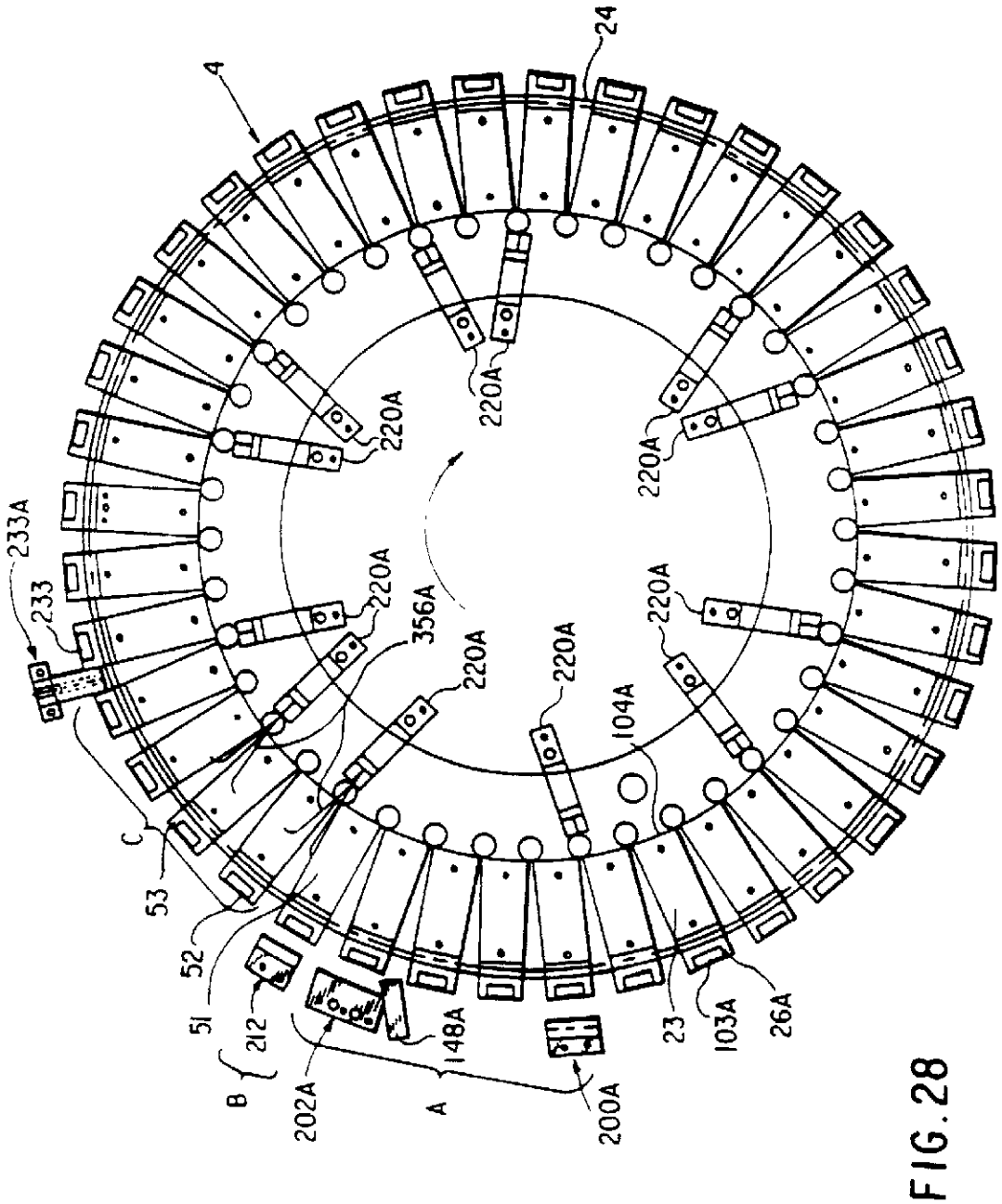


FIG. 27


4
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220A
233A
233
356A
104A
C
53
52
51
212
B
202A
148A
A
200A
23
103A
26A

FIG. 28

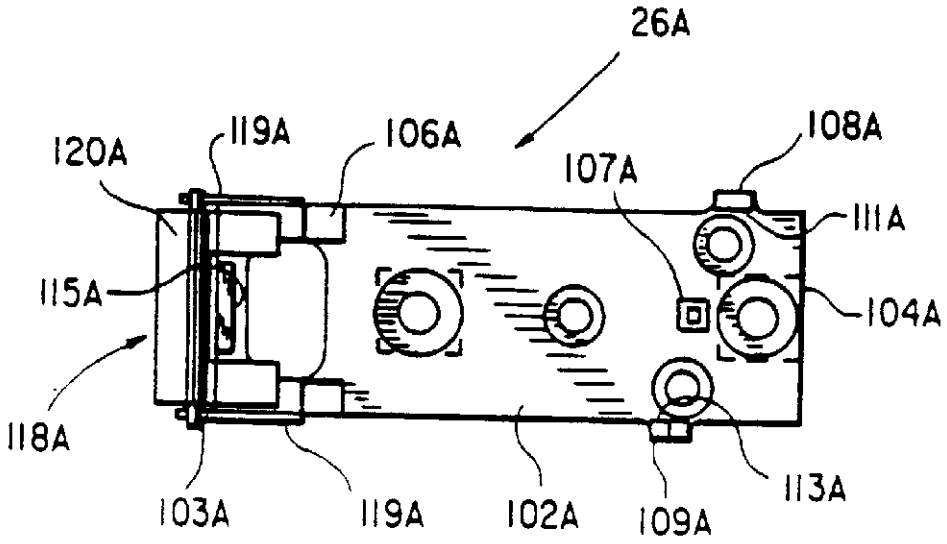


FIG. 29A

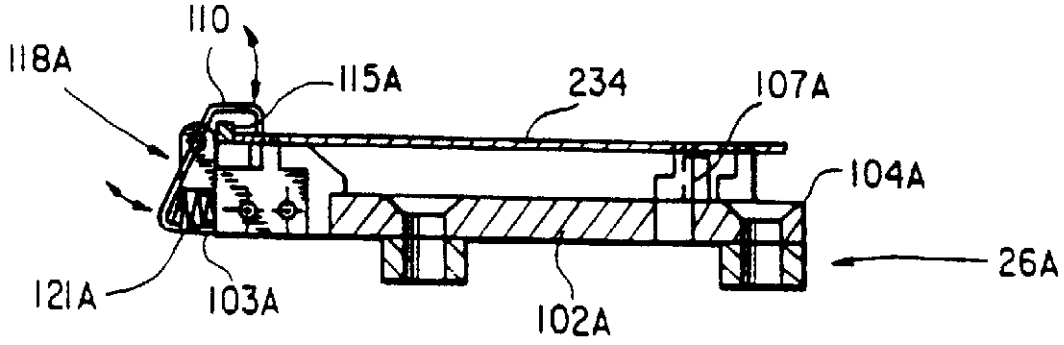


FIG. 29B

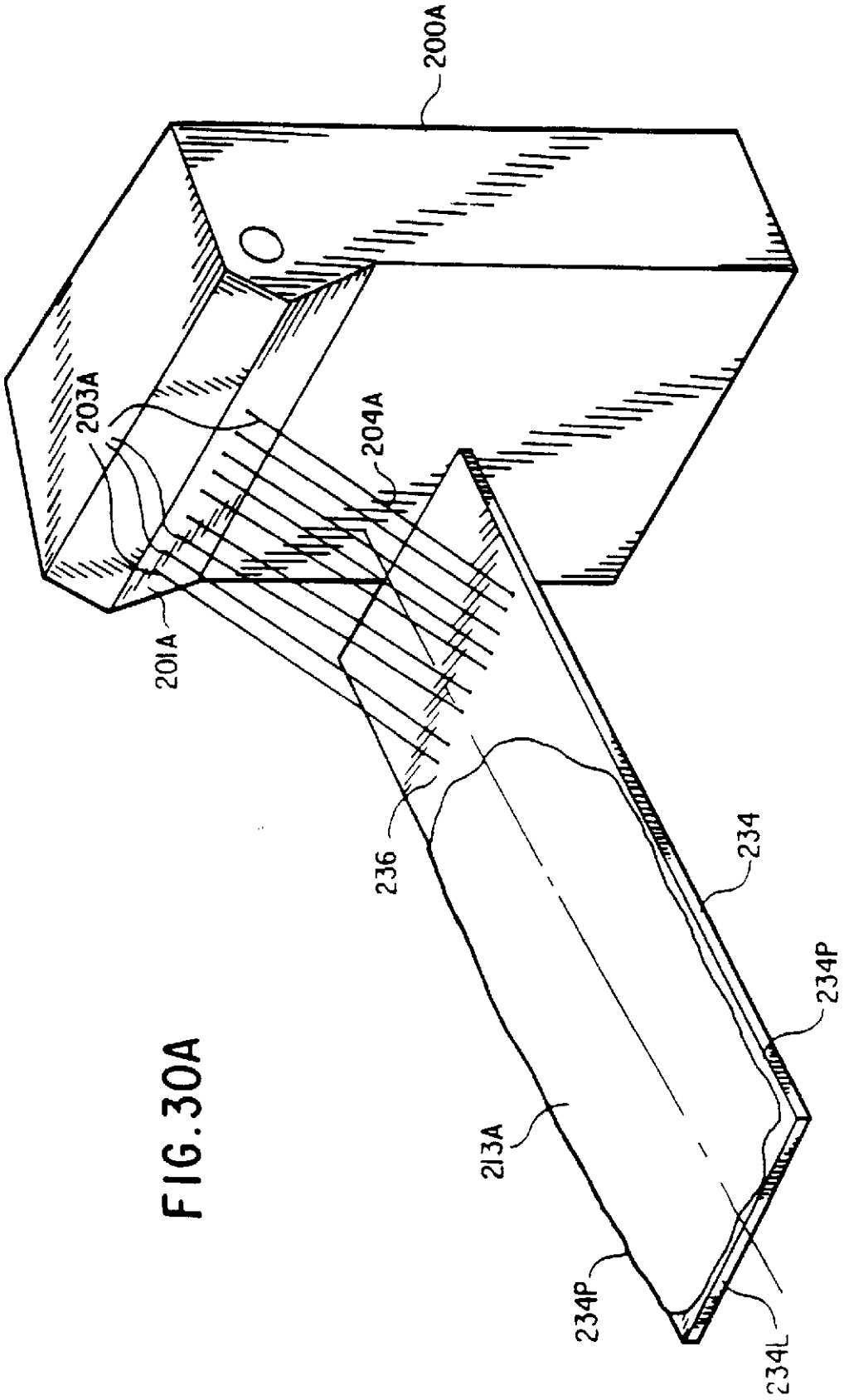


FIG. 30A

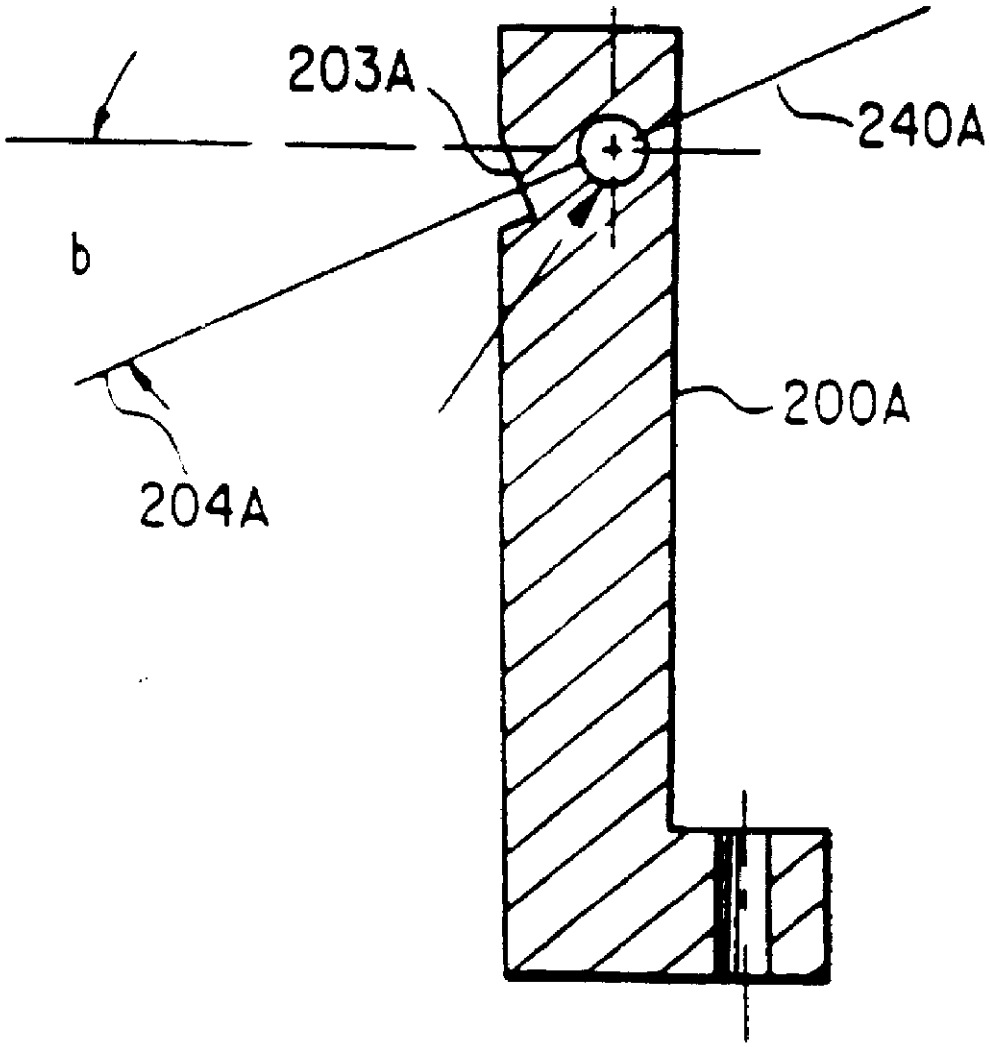


FIG. 30B

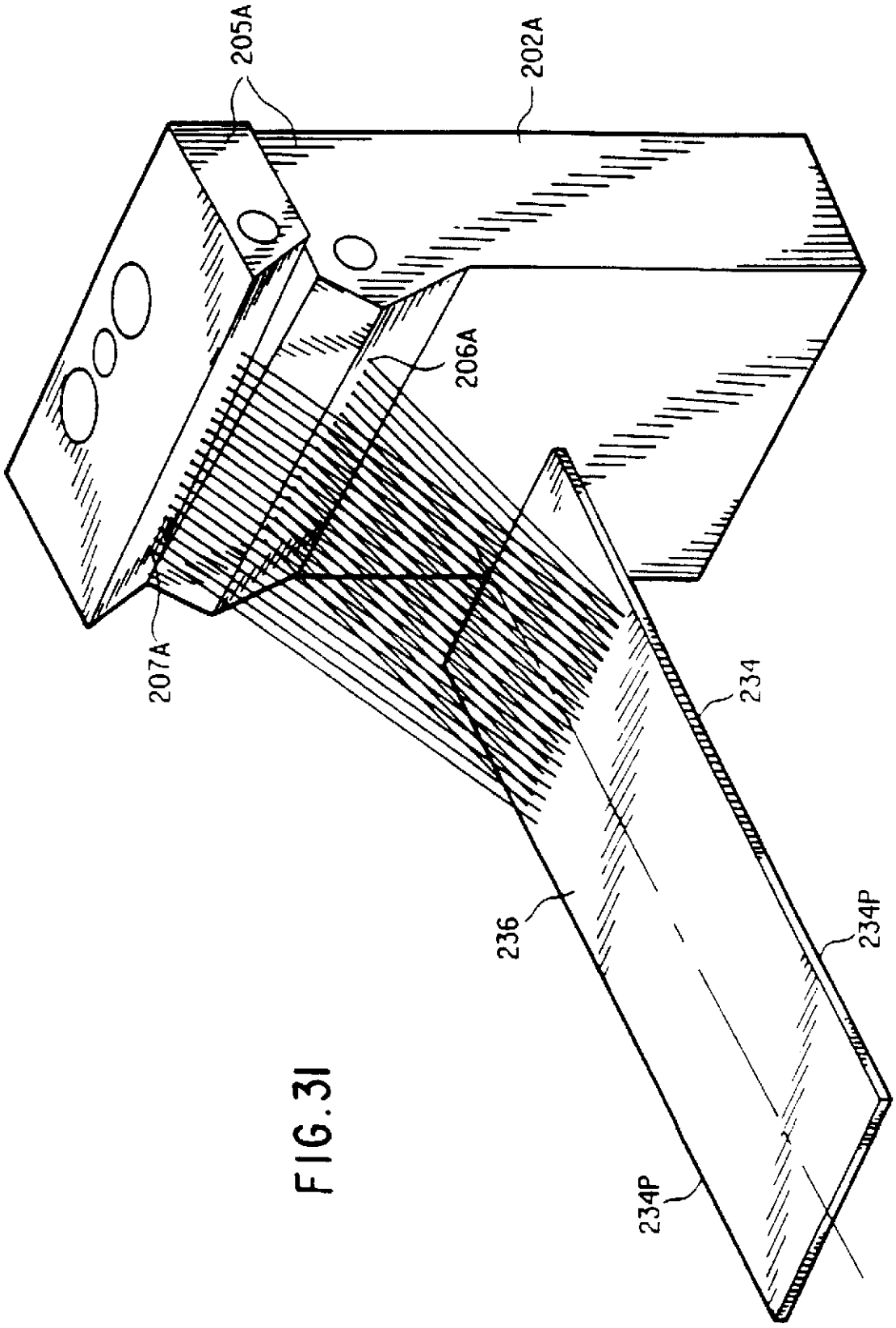
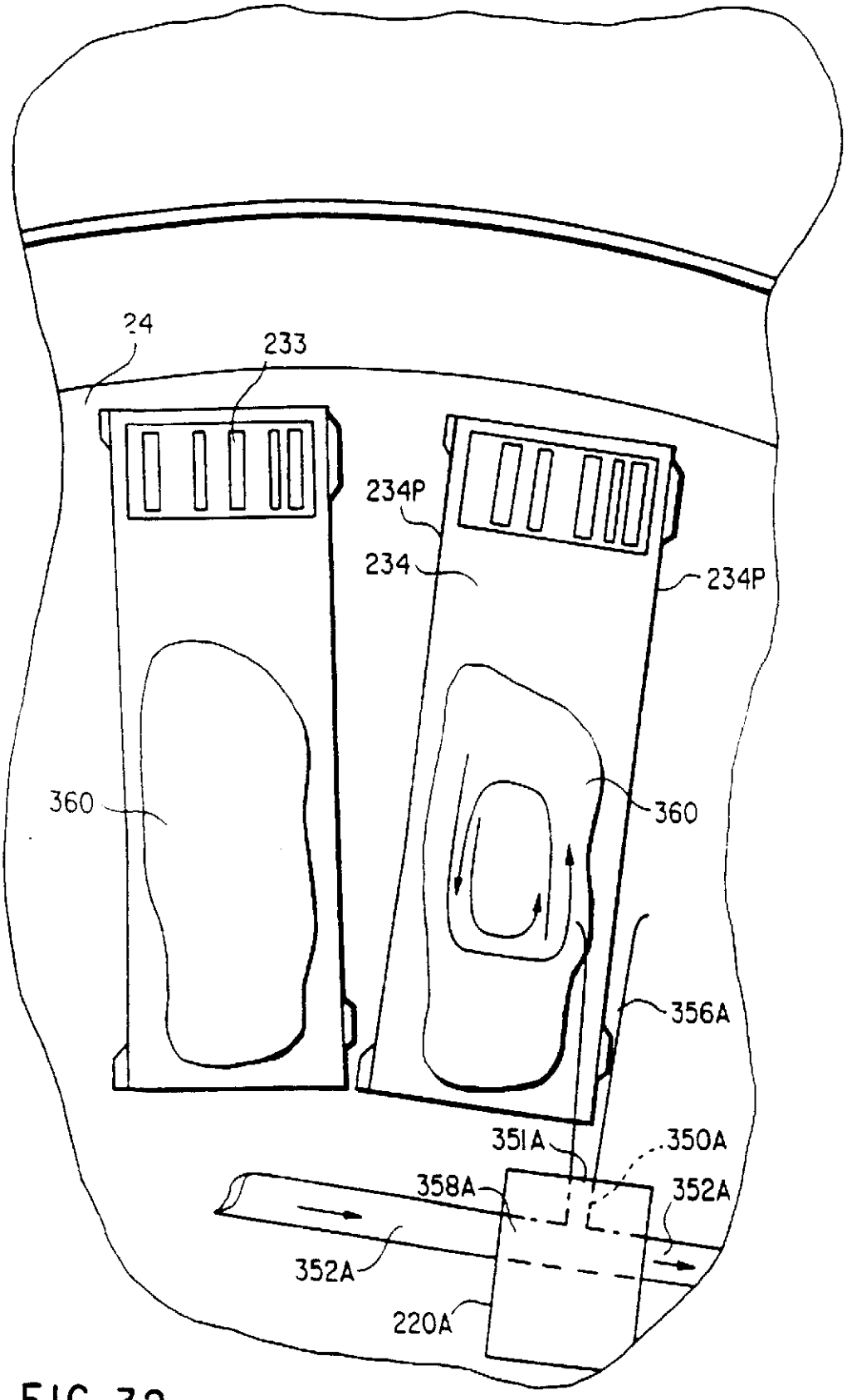


FIG. 31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234P
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351A
350A
358A
352A
352A
220A

FIG. 32

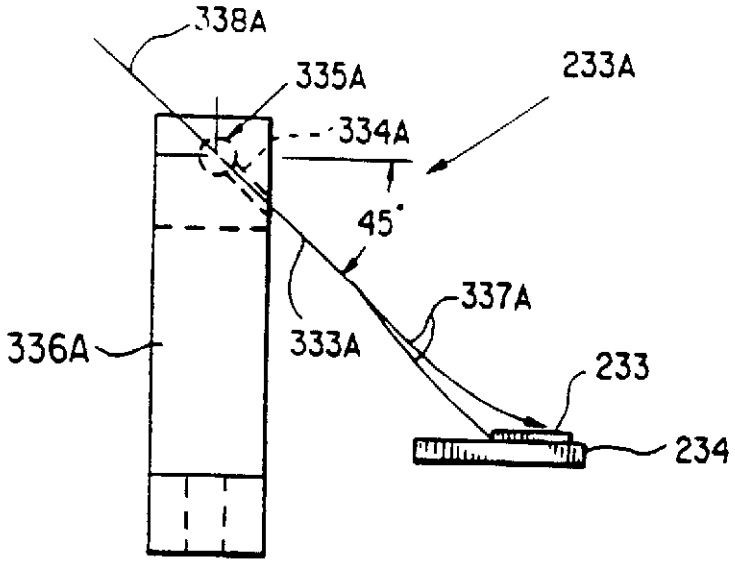

FIG. 33A

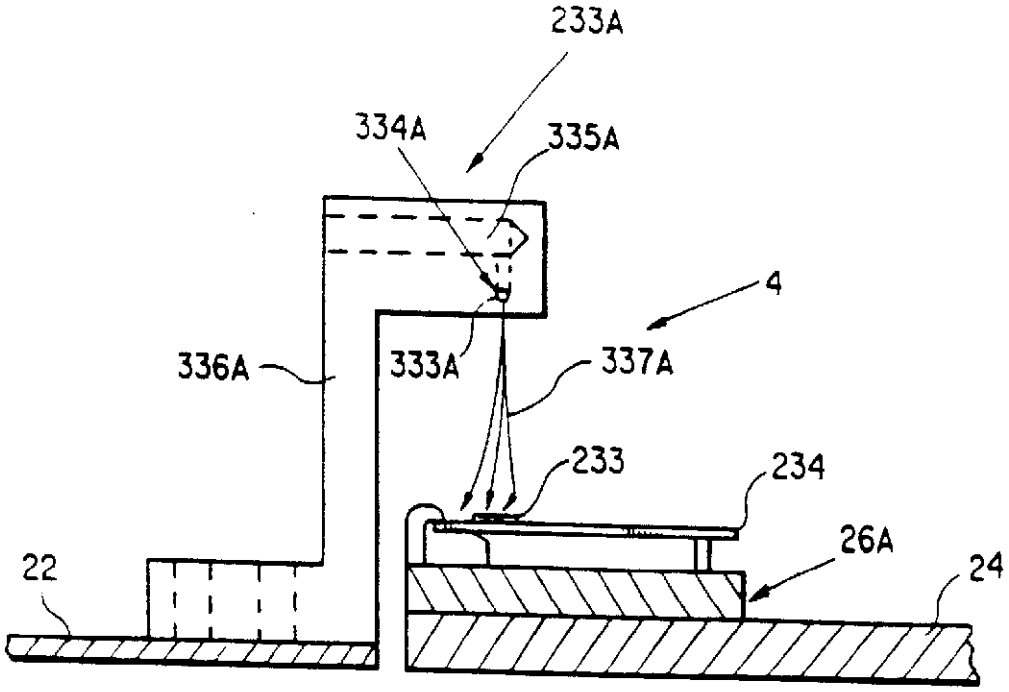

FIG. 33B

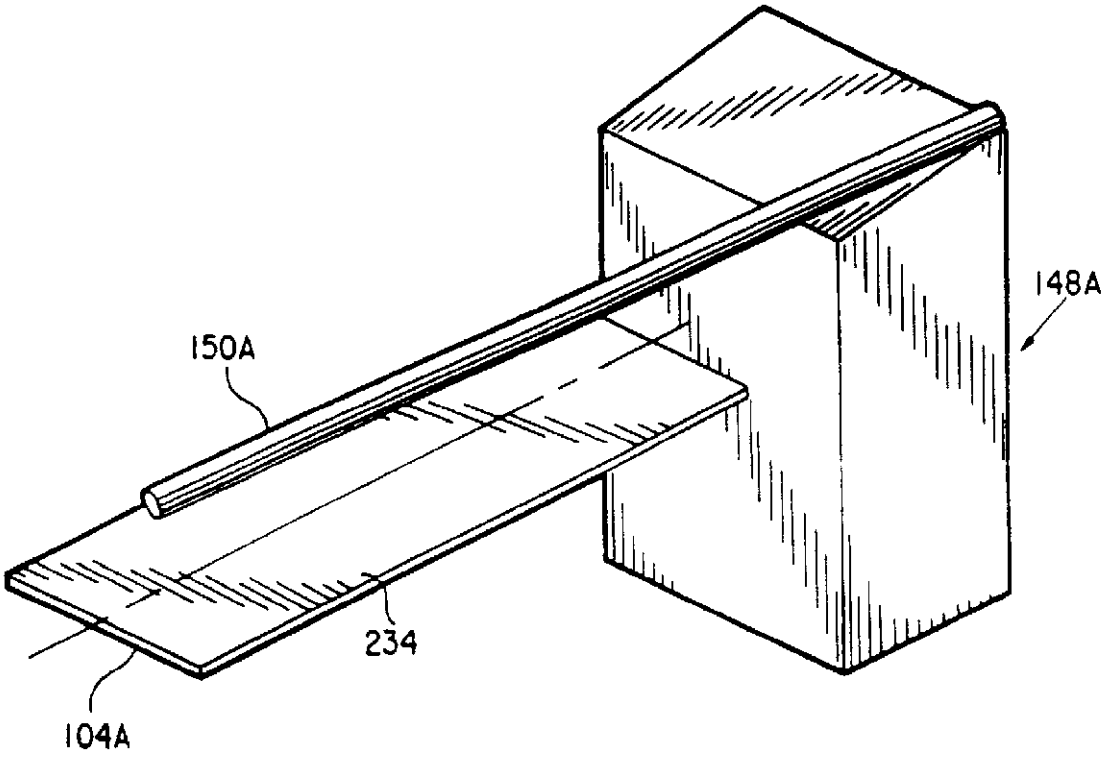

FIG. 34

AUTOMATED BIOLOGICAL REACTION APPARATUS

This is a continuation of application Ser. No. 08/906,678, filed Aug. 5, 1997, pending, which is a continuation of application Ser. No. 08/479,415, filed Jun. 6, 1995, U.S. Pat. No. 5,654,200, which is a division of application Ser. No. 08/352,966, filed Dec. 9, 1994, U.S. Pat. No. 5,595,707, which is a continuation of application Ser. No. 07/924,052, filed Aug. 31, 1992, abandoned, which is a continuation-in-part of application Ser. No. 07/488,601, filed Mar. 2, 1990, abandoned.

TECHNICAL FIELD

This invention relates an improved biological reaction platform which can be used for a wide variety of assays, for example, automatic immunostaining of tissue sections, in situ DNA analysis, immunoassays such as ELISA, and the like. The automatic device of this invention can be used to process a large number of samples such as tissue sections mounted on slide surfaces using agents and protocols preselected by the operator, while maintaining the slide surfaces in a substantially horizontal plane throughout the incubation cycles.

BACKGROUND ART

Immunostaining and in situ DNA analysis are useful tools in histological diagnosis and the study of tissue morphology. Immunostaining relies on the specific binding affinity of antibodies with epitopes in tissue samples, and the increasing availability of antibodies which bind specifically with unique epitopes present only in certain types of diseased cellular tissue. Immunostaining requires a series of treatment steps conducted on a tissue section mounted on a glass slide to highlight by selective staining certain morphological indicators of disease states. Typical steps include pretreatment of the tissue section to reduce non-specific binding, antibody treatment and incubation, enzyme labeled secondary antibody treatment and incubation, substrate reaction with the enzyme to produce a fluorophore or chromophore highlighting areas of the tissue section having epitopes binding with the antibody, counterstaining, and the like. Each of these steps is separated by multiple rinse steps to remove unreacted residual reagent from the prior step. Incubations are conducted at elevated temperatures, usually around 40° C., and the tissue must be continuously protected from dehydration. In situ DNA analysis relies upon the specific binding affinity of probes with unique nucleotide sequences in cell or tissue samples and similarly involves a series of process steps, with a variety of reagents and process temperature requirements.

Automated systems have been explored to introduce cost savings, uniformity of slide preparation, and reduction of procedural human errors. Stross, W. et al, *J.Clin.Pathol.* 42:106–112 (1989) describes a system comprising a series of baths positioned under the circumference of a circular, rotatable disc from which slide trays are suspended. The disc is lifted to lift slide trays from their baths, turned to position the slide trays above the next consecutive bath, and lowered to immerse the slide trays in the baths. This operation can be automated with suitable timers and switches. This system exposes each of the slides to the same treatment and relies on dipping for application of reactants and rinsing.

Stark, E. et al, *J.Immunol.Methods.* 107:89–92 (1988) describes a microprocessor controlled system including a revolving table or carousel supporting radially positioned

slides. A stepper motor rotates the table, placing each slide under one of the stationary syringes positioned above the slides. A predetermined volume of liquid, determined by a dial, is delivered to a slide from each syringe. Microprocessor controls are provided.

Cosgrove, R. et al, *ACL.* pp 23–27 (December, 1989) describe an immunostaining apparatus for auto-pipetting reagents into a slide well from a carousel holding up to **18** reagent vials. Below each well, a coverplate spaced from the surface of each slide provides cover and defines a reagent flow channel. The slides are suspended at a steep angle. Reagent from the well flows downward over the slide surface. A row of slides are suspended for sequential treatment. Washing is accomplished by a 3 to 4 minute continuous running wash over the sample, yielding an estimated 20:1 wash/reagent ratio.

Brigati, D. et al, *J.Histotechnology* 11:165–183 (1988) and Unger, E., Brigati, D. et al, et al, *J.Histotechnology.* 11:253–258 (1988) describe the Fisher automated work station using capillary gap technology. A coverplate is placed over the slide, forming a capillary gap. Liquid is introduced into the capillary gap by placing the lower edge of the plate-slide pair in a liquid. Liquid is removed by placing the lower edge of the plate-slide pair on a blotter. The system is further described in U.S. Pat. Nos. 4,777,020, 4,798,706 and 4,801,431. The previously known devices are limited in their performance and unable to satisfy the needs for automated, high precision immunohistology.

It is an object of this invention to provide a device which provides more rapid, reliable and more reproducible results than standard methods; can perform any standard immunochemical assay including assays relying on immunofluorescence, indirect immunoassay procedures, peroxidase anti-peroxidase methods, or avidin-biotin technology; preforms all steps of the immunohistochemical assay irrespective of complexity or their order, at the time and temperature, and in the environment needed; and is cost effective in terms of equipment, reagent and labor costs.

DISCLOSURE OF THE INVENTION

The automated biological processing apparatus of this invention comprises a reagent carousel cooperating with a sample support carousel to apply a sequence of preselected reagents to each of the samples with interposed mixing, incubating, and rinsing steps cooperating therewith. The slide support carousel has a plurality of slide supports thereon and drive means engaging the slide support carousel for consecutively positioning each of a plurality of slide supports in a reagent receiving zone. The reagent carousel has a plurality of reagent container supports thereon and drive means engaging the reagent carousel for rotating this carousel and positioning a preselected reagent container support and associated reagent container in a reagent supply zone. The apparatus has a reagent delivery actuator means positioned for engaging a reagent container positioned on a container support in the reagent supply zone and initiating reagent delivery from the reagent container to a slide supported on a slide support in the reagent receiving zone.

The apparatus preferably has bar code readers positioned to read bar codes on the sample containers or slides and on the reagent containers. Each of the carousels have homing systems containing a detectable component and a proximity detector therefor for indexing the position of the reagent containers and slides.

One particular advantageous feature of the present invention is that by employing a computer control arrangement to

control the positioning of the reagent and slide support carousel, different reagent treatments can be individually performed for each of the various tissue samples by appropriate programming of the apparatus. Additionally, the provision of the bar code readers permits tracking of each of the tissue samples as well as a record of the reagents applied thereto.

The apparatus preferably has a heating chamber means surrounding the slide support carousel for heating slides supported thereon to a predetermined temperature. The heating chamber means includes a hot gas manifold having a plurality of hot gas outlets positioned above the slide supports. The heating chamber means includes a temperature sensor and a hot gas control means connected to the temperature sensor for increasing heat supplied to gas flowing through the manifold and for increasing the hot gas flow rate if further heat is required to maintain the heating chamber at a preselected temperature. The temperature sensor is a thermistor, the tip thereof being enclosed in a heat sensitivity reducing jacket. The hot gas control system includes two heating components with separate controls and a speed control for the hot gas fan.

The drive means engaging the slide support carousel is also a means for consecutively positioning each of a plurality of slide supports at rinse zone, an evaporation control liquid and reagent receiving zone, a vortex mixing zone including vortex mixing means, and an incubation zone formed by the heating chamber means.

According to a first embodiment of the rinse zone, rinse spray means are positioned adjacent to the rinse zone for applying pulses of rinse liquid to the surface of each of the slides positioned in the rinse zone. The apparatus slide supports are, according to this first embodiment of the rinse zone, pivotally mounted for pivotal motion from a horizontal slide incubation position to a tilted slide draining position following each pulse of rinse liquid.

According to a second embodiment of the rinse zone, first and second rinse spray means are respectively positioned only at the beginning and end of the rinse zone, so as to be spaced from one another. The first rinse spray means deposits a layer of rinse liquid onto a slide upon entering the rinse zone and the second spray means, after a predetermined waiting period, uses pulsed streams of rinse liquid, alternately directed at the longitudinal edges of the slides, to knock the previously deposited layer of rinse liquid off of the slide as the slide exits the rinse zone. According to this second embodiment of the rinse zone, the apparatus slide supports are stationary, a jet drain being provided at, for example, the end of the rinse zone, which directs a stream of fluid, such as, for example, air or the like, over the slide to drain any remaining rinse liquid off of the slide surface.

The apparatus preferably has a volumetric pump means, and a reagent delivery actuator means positioned for activating the volumetric pump means, thereby effecting delivery of reagent from a reagent container by the volumetric pump to the reagent delivery zone. An evaporation inhibitor liquid application means is positioned adjacent the reagent delivery zone.

Vortex agitation means are positioned adjacent the agitation zone for stirring reactants on a slide supported in the vortex agitation zone.

The pivoting slide support has distal and proximal ends, the distal end having raised terminal and lateral distal guide tabs with guide termini. The proximal end has first and second lateral guide tabs with opposed slide engaging surfaces for engaging and holding the lateral edges of a slide. The guide termini are lower than the upper slide surface plane. In this embodiment of the slide support, the slide support surface is tipped or pivoted by a tipper to drain rinse liquid from the surface of the slide.

The stationary slide support has a slide support platform at a proximal end and a slide support post at a distal end thereof. The distal end also has raised lateral distal guide tabs with guide termini between which a slide is positioned. The slide support platform at the proximal end has a guide edge and a slide clamping arrangement for clamping a slide to the support platform without interfering with the reading operation of the bar code reader. The distal guide termini are lower than the upper slide surface plane to prevent wick-off of liquid on the slide surface. In this embodiment, rinse liquid is drained from the surface of the slide employing a jet drain which directs a stream of fluid, i.e., gas or liquid, over the slide surface.

An improved biochemical method of this invention with increased sample dehydration protection comprises carrying out a biochemical reaction under a layer of evaporation inhibiting liquid. The improvement comprises (a) covering the sample with an aqueous surface layer by applying an aqueous solution to a planar support surface adjacent a biological sample mounted thereon; and (b) covering the aqueous surface layer with an evaporation inhibiting liquid layer by applying the evaporation inhibiting liquid to the planar support surface adjacent the biological sample in an amount sufficient to form a continuous layer of evaporation inhibiting liquid over the sample. The evaporation inhibiting liquid is substantially water-insoluble, substantially water-immiscible and substantially non-viscous; has a specific gravity less than water, and a boiling point above 50° C.; and is devoid of chemical characteristics which would significantly interfere with biochemical reactions carried out on the sample. The biological sample can then be optionally treated (c) with an aqueous reagent solution by applying the reagent solution to the planar support surface adjacent the biological sample. The reagent solution flows to the biological sample under the evaporation inhibiting liquid layer, and the sample is continuously protected from dehydration by the evaporation inhibiting layer.

In another aspect of this invention, the reagent solution is stirred on the surface of the biological sample by applying at least one gas stream to an area of the surface of the evaporation inhibiting liquid layer between the center of the evaporation inhibiting layer and the edge of the planar support surface, the gas stream having a central axis forming an acute angle with the planar support surface. According to one embodiment of the present invention, the reagent solution is preferable stirred by a vortex formed by applying two off-center gas streams, flowing in opposite directions, to the surface of the evaporation inhibiting liquid layer. According to a further embodiment of the present invention, the reagent solution is stirred by a vortex formed by applying a single gas stream along a longitudinal edge of the slide, the gas stream originating from the distal edge of the slide.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a left front, isometric view of the automated immunostaining apparatus according to a first embodiment of this invention which employs a tipper rinse method, with the cabinet shell removed.

FIG. **2** is an exploded right front isometric view of the apparatus shown in FIG. **1**.

FIG. **3** is a partial exploded left front isometric view of the apparatus shown in FIG. **1**.

FIG. **4** is a partial exploded right rear isometric view of the apparatus shown in FIG. **1**.

FIG. **5** is a top view of a pivotally mounted slide support.

FIG. **6** is an isometric view of the underside of the slide support component.

FIG. **7** is a side view of the pivotally mounted slide support of FIG. **5** showing the tipper and mounting details.

FIG. **8** is an isometric view of the mounted slide support of FIG. **7** in the untipped position.

FIG. **9** is an isometric view of the mounted slide support of FIG. **7** in the tipped position.

FIG. **10** is a distal end view of the mounted slide support in the tipped position.

FIG. **11** a fragmentary top view of the slide support carousel showing details of the slide treatment stations.

FIG. **12** is a schematic cross-sectional view of a rinse station taken along the line A—A in FIG. **11**, showing details of rinse liquid flow on a slide.

FIG. **13** is a top schematic view of the rinse stations showing details of the rinse liquid distribution on slides being treated therein.

FIG. **14** is an isometric view of the slide treatment bar code reading, rinse, reagent receiving and vortex mixing stations.

FIG. **15** is a schematic, fragmentary cross-sectional view of the evaporation inhibiting liquid and reagent receiving station, taken along the line B—B in FIG. **11**.

FIG. **16** is a cross-sectional view of the vortex mixing assembly, taken along the line C—C in FIG. **11**.

FIG. **17** is a top schematic view of the vortex mixing zone, showing details of the vortex mixing action.

FIG. **18** is a schematic representational cross-sectional view of a slide following the rinse liquid, evaporation inhibitor and reagent application steps.

FIGS. **19A–19B** are cross-sectional views of respective alternative embodiments of a rinse liquid container and associated heating components.

FIG. **20A** is a bottom, isometric view of one embodiment of a reagent container support tray.

FIGS. **20B–20C** are side sectional views of a further embodiment of the reagent container support tray.

FIG. **21** is a fragmentary cross-sectional view taken along the line D—D in FIG. **11** showing the slide carousel metal proximity sensor indexing system of this invention.

FIG. **22** is a schematic view of the pneumatic system of the automated immunostaining apparatus of this invention.

FIG. **23** is a schematic drawing of the 120 volt AC power distribution in the apparatus of this invention.

FIG. **24** is a schematic drawing of the DC power distribution in the apparatus of this invention.

FIG. **25** is a schematic drawing of a first portion of the computer digital I/O system in the apparatus of this invention.

FIG. **26** is a schematic drawing of a second portion of the computer digital I/O system in the apparatus of this invention.

FIG. **27** is schematic drawing of the computer serial and floppy disk I/O system in the apparatus of this invention.

FIG. **28** is a further embodiment of the intermediate section of the apparatus of this invention which dispenses with the tipper rinse method.

FIGS. **29A–29B** are top and side views respective an alternative embodiment of the slide support for use with the embodiment of FIG. **28**.

FIG. **30A** is a side, isometric view of one embodiment of a single wash block nozzle for use with the embodiment of FIG. **28**.

FIG. **30B** is a side, cross-sectional view of the single wash block nozzle of FIG. **30A**.

FIG. **31** is a side, isometric view of one embodiment of a dual wash block nozzle for use with the embodiment of FIG. **28**.

FIG. **32** is a top view of a further embodiment of the vortex mixers for use with the embodiment of FIG. **28**.

FIGS. **33A–33B** are side and front views respectively of bar code cleaning arrangement for use with the embodiment of FIG. **28**.

FIG. **34** is a schematic of a jet drain for draining liquid from an upper surface of a slide.

BEST MODE FOR CARRYING OUT THE INVENTION

The automated immunostaining apparatus of this invention preforms all steps of immunohistochemical and in situ DNA assays irrespective of complexity or their order, at the time and temperature, and in the environment needed. Specially prepared slides containing a bar code identifier and a mounted tissue section are placed in special support on a carousel, subjected to a preprogrammed sequence of reactions, and are removed from the carousel, ready for coverslipping and histological examination. For purposes of clarity of the following description of the apparatus of this invention and not by way of limitation, the apparatus will be described in terms of immunohistochemical processes.

FIG. **1** is a front right, isometric view of the automated immunostaining apparatus of this invention, with the cabinet shell removed. Liquid and air supply tubing and electrical wiring connecting the respective components are conventional, well known in the art, and are omitted from the drawings for purposes of clarity. The apparatus has an upper section **2**, intermediate section **4** and lower section **6**. In the upper section **2**, reagent bottle support carousel **10** is mounted for rotation about its central axis **7** on upper support plate **8**. Reagent bottles **12** required for the immunohistochemical reactions to be conducted during slide treatment cycle are supported by the carousel **10**, mounted in reagent bottle receptors **11**. These receptors **11** are configured to receive volumetric pump outlet tube **307**, shown in detail in FIG. **15**. The receptors **11** are preferably equally spaced in a circular pattern axially concentric with the carousel axis **7**. The number of receptors **11** provided should be sufficient to accommodate the number of different reagent bottles **12** required for a cycle or series of cycles. Twenty-five receptors **11** are shown, but the number can be smaller or greater, and the diameter of the carousel **10** can be increased to accept a larger number of reagent bottles **12**. The carousel **10** is rotated by the stepper motor **14** drive belt **16** to a position placing a selected reagent bottle **12** in the reagent deliver position under the air cylinder reagent delivery actuator **18** over a slide to be treated with reagent. Reagent tray motor driver **20** is connected to stepper motor **14**.

The intermediate section **4** comprises support plate **22** upon which the slide support carousel **24** is rotatably mounted. The carousel **24** supports slide supports **26**. Heated air supply chamber **28** communicates with the heated air supply manifold **30** supported on the underside of plate **8** and lid heated air supply manifold **31** mounted on the upper plate **8** by hinged supports **33**. The support plate **22** also supports the conventional computer board **32**, LCD display

34, disk drive 35 and computer 36 used to operate the apparatus. Air pressure regulator 38, as best seen in FIG. 2, regulates the pressure of air delivered to the evaporation inhibitor and rinse liquid delivery systems described in FIG. 22.

The lower section 6 includes support plate 40 upon which are supported accessories such as power supply filter 42 and hot water supply 44.

FIG. 2, FIG. 3 and FIG. 4 are exploded right front, left front and right rear isometric views of the apparatus shown in FIG. 1. Tipper air cylinders 46 are positioned on support plate 8. These cylinders are aligned to actuate a tipper cam surface 148 against a slide support tab surface 112 shown in detail in FIGS. 8, 9 and 10.

In the intermediate section 4, the stepper motor 48 rotates the slide support carousel 24, engaging drive belt 25 (FIGS. 3 and 4) engaging the perimeter of the slide support carousel 24. Splash guard 50 is a wall which surrounds the sides, back and part of the front of the carousel 24, defines the heating zone and contains the liquid spray and droplets produced in the processing. It extends upward from the intermediate plate 22 to a position adjacent the upper plate 8, leaving an air flow gap between the upper edge of the splash guard 50 and the underside of the plate 8. Mounted on the underside of upper support plate 8 above the carousel 24 and within the perimeter of the splash guard 50 is the heated gas supply manifold 30 (FIG. 2). Heated air is directed downward and over the slide supports 26 by holes 336 (FIG. 15) in the manifold 30. The heated air then passes upward over the top of the splash guard 50 and exits the device. Extending upward through central opening 52 of carousel 24 into the heated air supply chamber 28 is the fan shroud 54 and axially positioned fan 56. The fan 56 is positioned over air vents 57 in the bottom plate 22. The annular waste liquid sump 58 surrounds the shroud 54, below liquid outlet ports 292 (FIG. 14), and is supported on the bottom of plate 22. The waste reagent and rinse liquids are collected in the sump and passed to a drain through an outlet tube in the sump bottom (not shown).

Rinse and liquid coverslip spray blocks 60 are supplied with liquid through conventional solenoid valves 62.

Temperature controller 66, mounted on support plate 22, controls the heat energy supplied to the heated water container 44. Temperature controllers 68 and 70, mounted on support plate 40 (FIG. 4), control the temperature of the air in the heated air supply chamber 28 by controlling energy supplied to respective annular heater elements 331 and 332 (FIG. 15). Slide carousel stepper motor driver 72 and relay 74 operate stepper motor 48. Power supplies 76 and 78 provide power to the stepper motors and control systems. Air compressor 80 supplies air to the air filter 82 and air pressure regulators 38, 64 and 86.

FIG. 5 is a top view of a first embodiment of a mounted slide support 26 with slide edges 100 and 101 represented by dashed lines. The slide support 26 has a support plate 102 with a distal end 103 and a proximal end 104. The distal end 103 has a raised terminal guide end tab 106 and two lateral guide tabs 108 and 110 with the upper edges constituting guide tab termini. The distance between the upper surface of the slide support 26 and the guide tab termini (the elevation above the upper surface) is less then the thickness of a conventional microscope slide. The proximal end 104 of the slide support 26 has opposed lateral guides 112 and 114 for engaging the lateral edges of a slide and a terminal end tab 115 for engaging the proximal end of a slide. The proximal end 104 of the slide support 26 has an inflexible support portion 116 providing a lateral edge 120 and a flexible arm 118 including a lateral edge 122 positioned such that lateral edges 120 and 122 oppose one another. The distance between the slide edge engaging surfaces 111 and 113 of the guide tabs 112 and 114 is less than the width of a slide to be supported on the slide support 26. A standard slide has a width of 1 inch or 25 mm, and the preferred distance between the slide edge engaging surfaces 111, 113 of the tabs 112, 114 for supporting a standard slide is from 20 to 24 mm. The flexure of arm 118 permits positioning of the slide between the lateral guide tabs and terminal end tabs 106, 115. The distance between the opposing tab surfaces 111 and 113 causes the slide support 26 to apply a positive pressure on the edges of a slide, retaining the slide securely on the slide support 26 during the tilting and other processing steps. The upper surface of the support plate 102 is preferably planar and smooth so the wet slide rests closely on the surface 102, and surface tension will resist vertical movement of the slide from the support surface 102.

FIG. 6 is an isometric view of the underside of the slide support 26. The inflexible portion 116 has an integral pivot support 124 which reinforces the inflexible portion 116 to prevent flexure. The flexible arm 118 has sufficient depth or thickness to limit the flexural movement of the arm 118 to a horizontal direction. This insures effective cooperation and pressure between the guide tab 112 on the inflexible portion 116 and the guide tab 114 on the flexible arm 118 to assist in retaining the slide in place on the slide support 26 during the tipping operation described in detail hereinafter.

FIG. 7 is a side view of a mounted slide support showing the tipper and mounting details. The upper pivot support 124 is pivotally mounted on the lower pivot support 126. Lower pivot support 126 has upward extending projections 128 and 130 which engage the ends 132 and 134 of the upper pivot support 124. Pivot pin 136 extends through an axially aligned hole in projection 128 into an axially aligned receptor hole 138 (FIG. 6) in the opposing end 132 of the upper pivot support 124. At the opposite end, axially concentric with pivot pin 136, pivot pin 140 extends through a hole in projection 128 (not shown) into a respective receptor hole in the opposing end 134 of the upper pivot support 124. The slide support 102 is thus mounted for pivotal motion around the common pivot axis of the pins 136 and 140. Bias spring 142 is supported on pin 134, one end 141 pressing against the lower abutment surface 143 of the inflexible support portion 116, and the other end 144 bearing against spring stop groove 145 in the spring stop 146. The tip 148 of tipper 150 is positioned above the upper surface of guide tab 112 when the slides are positioned in a rinse station, described in greater detail hereinafter with respect to FIG. 13.

The pivot pins 136 and 140 support the upper surface of the slide support 102 at a small angle 'a' from the horizontal plane to aid liquid flow toward the distal end 103 during treatment. Angle 'a' is preferably in the range of from 0.3 to 1.0°. The upper surface 151 of the inflexible support portion 116 and the upper slide surface 152 (dotted line) supported thereon are thus maintained at a slight incline from the horizontal plane downward toward the distal end 103 of the slide support 26.

FIG. 8 is an isometric view of a slide (dashed lines) mounted on slide support 26 in the untipped position, FIG. 9 is an isometric view of the mounted slide support 26 in the tipped position, and FIG. 10 is a distal end view of the mounted slide support 26 in the tipped position. Vertically downward pressure of the tipper tip 148 against the upper guide tab surface 154 of guide tab 112 rotates the support plate 102 about the pivot axis 156 defined by the pivot pins

136 and 140. The pivot axis 156 (FIG. 5) preferably lies in a vertical plane through the midpoint of distal end 103 and the left edge proximal end 104 of the slide support 26. The tipping action tilts the slide surface to an angle 'c' of approximately 60° from the vertical (FIG. 10). It sharply lowers distal corner 158 and sharply raises proximal corner 160, breaking the liquid meniscus on the slide surface and directing the liquid flow 159 to the corner 158 and off the surface of the slide into drain hole 292. The pivotal movement increases the pressure of the spring 142 against spring stop groove 145, and as the tipper 150 is raised, the slide support 25 returns to its original position. The slide support return pivot motion is terminated when distal corner 162 of the support plate 102 abuts stop surface 164 of the lower pivot support 126.

FIG. 11 a fragmentary top view of the slide support carousel 24 showing details of the various slide treatment stations. Rinse nozzle blocks 200, 202 and 204 and the adjacent respective slides 206, 208 and 210 define successive rinse zones, details of which are shown in FIGS. 12–14. Evaporation inhibitor liquid application block 212 and the adjacent slide 214 define the evaporation inhibitor and reagent application zone, details of which are shown in FIG. 15. Air cylinder reagent delivery actuator 18, supported by support arm 216, contacts reagent bottle 218, directly over slide 214. Vortex mixer air jet blocks 220, 222 and 224 are positioned adjacent slides 226 and 228 in the agitation zone, details of which are shown in FIG. 16 and 17. The hanger 352 is mounted on the tip of blocks 220 and 222 and supports suspended block 224. Pressurized air is delivered to block 224 by conduit 358. As the slide support carousel 24 positions each slide for successive treatment in the rinse zones, evaporation inhibitor and reagent application zone, and agitation zones (counter-clockwise movement of the carousel), the tissue sections on each slide are first rinsed and then covered with evaporation inhibitor. Reagent is applied from a preselected reagent bottle to the tissue through the evaporation inhibitor layer, and the reagent is agitated through the evaporator inhibitor layer by the vortex mixer. Each slide then is moved around the incubation zone, a circular path traveled by the slide support carousel 24, heated with hot air from the heated air manifold 30, and the reagent reacts with the sample. As the carousel 24 continues to increment around the circle, each slide is returned to the rinse stations, etc, for application of the next reagent required in the reaction. This entirely automated progress continues until the desired reactions are completed.

Bar code reader 231 (FIG. 14) above slide 205 reads a slide bar code 233 (FIGS. 13 and 17) on each slide. The slide bar codes 233 identifies the slide sample and the particular immunohistochemical process required for that sample. This information is fed into the computer and correlated with the indexed position of that slide with respect to "home", to control the sequence of reagent chemicals to be applied to that slide in the reagent application zone.

FIG. 12 is a schematic cross-sectional view of a rinse station taken along the line A—A in FIG. 10, showing details of rinse liquid flow on a slide. Rinse block 200 mounted on plate 22 has a heated rinse liquid supply channel 230 communicating with rinse liquid nozzle 232. The slide 234 has a sloping surface at an angle 'a', being supported on the sloping surface of the slide support 102. The slide 234 has a rinse liquid impact zone 236 adjacent the proximal end 104 between the bar code 233 and the sample 238. The impact zone 236 is at a higher elevation than the tissue section 238 supported adjacent the distal end 103. The nozzle axis 240 has an angle 'b' which directs liquid against the slide surface impact zone 236. The impact zone 236 is above the tissue section 238 on the sloped surface of slide 240, and the rinse liquid stream 242 flows across the upper surface of the tissue section 238 toward the distal end 103. The angle 'b' preferably has an angle of from 15 to 35°, and the distance between the exit of nozzle 232 and the slide 124 is selected to direct the rinse liquid precisely on the impact zone 236, avoiding disturbance of the fragile tissue section 238.

The slide support carousel 24 is rotated above the plate 22, the outer periphery being supported by low friction slide bearings 244 arrayed in an axially concentric circular path on plate 22 under the outer periphery of carousel 24.

FIG. 13 is a top schematic view of one embodiment of the rinse stations showing details of the rinse liquid distribution on slides being rinsed therein. Slides 234, 246, and 248 are positioned in the path of heated rinse solutions (dotted lines) from rinse station blocks 200, 202 and 204. Fragile tissue sections 238, 250 and 252 are positioned adjacent the distal end of the slides. The rinse liquid impact zones 236, 254 and 256 are positioned between the tissue sections and the proximal ends of the slides, to avoid direct impact of the liquid jets from the rinse block nozzles. The rinse nozzles on each block are preferably 11.5 mm apart. Rinse block 200 has right offset nozzles 232 and 258 (offset 2 mm to the right of center) supplied by channel 230 connected to supply tubing 260. This directs the rinse fluid toward the right surface of the slide, effecting a transverse flow path across the tissue section 238 to the distal end drain corner 158. Rinse block 202 has symmetrical nozzles 262 and 264 supplied by channel 266 connected to supply tubing 268. The symmetrical nozzle configuration effects a central flow path across the tissue section 250. Rinse block 204 has left offset nozzles 270 and 272 (offset 2 mm to the left of center) supplied by channel 274 connected to supply tubing 276. The left offset nozzles 270 and 272 direct a rinse flow path down the left side of the tissue section 252. The nozzle patterns provide effective rinse solution flow distribution across all portions of the tissue section surface as the slide is treated in each successive rinse section.

FIG. 14 is an isometric view of the rinse stations, a evaporation inhibiting liquid and reagent application station, and agitation stations, showing details of the slide tipping action in the rinse sections. Tipper air cylinders 46 (FIG. 3 and 4) comprises three conventional air cylinders 278, 280 and 282 with internal pressurized air activated pistons or equivalent actuators. Pressurized air delivery to the cylinders causes respective tipper tips 148, 284 and 286 to move downward, pressing against respective slide support tabs 112, 288 and 290. Three tipper positions are shown to illustrate the action thereof. Tipper tip 148 is shown in the fully withdrawn or resting position, and slide 206 is in the rinse solution receiving position. After application of heated rinse solution, the tipper descends through an intermediate position shown by tipper tip 284 and slide support 208, to the drain position shown by tipper tip 286 and slide support 210. Liquid drains from the left distal corner (lowest corner) into a drain hole 292.

In each rinse station, the sample is treated with a repeated, preferably at least seven, rinse cycles. Each rinse cycle comprises application of approximately 500 μL of heated rinse solution in a short pulse (120 msec) to the slide, followed by tipping the slide to drain away the rinse solution. An estimated 150 μL of liquid remains on the slide after draining. These rinse cycles are repeated in each rinse station. The short rinse pulse followed by draining prevents the formation of a equilibrium solute boundary layer and greatly increases the rinse efficiency, overcoming the bound-

ary problems present in the prior art rinse methods. Assuming that 150 μL of rinse solution is left after each draining step, a 23 percent dilution is achieved with each rinse cycle. Thus the effective dilution in the combination of the three rinse stations is estimated to be 0.2 parts per trillion, many orders of magnitude more effective than prior art, biochemical rinse procedures. This greatly increases the sensitivity of the immunohistological process.

FIG. **15** is a schematic, fragmentary cross-sectional view of the evaporation inhibiting liquid and reagent application station, taken along the line B—B in FIG. **11**. Evaporation inhibitor liquid distributor block **212** has a supply channel **293** and outlet nozzles **294**.

The evaporation inhibiting liquid is substantially water-insoluble, substantially water-immiscible and substantially thin or non-viscous. It has a specific gravity less than water, and a boiling point above the process temperature, preferably above 100° C. It should be devoid of chemical characteristics which would significantly interfere with biochemical reactions carried out on the sample, that is, the reactions taking place between the reagents and tissue sample on the slide. Preferred evaporation inhibiting liquids are hydrocarbons, optimally non-aromatic saturated hydrocarbons, having from 9 to 18 carbons, most optimally having about 10 to 14 carbon atoms.

A small quantity of evaporation inhibitor liquid is directed by nozzle **294** in a inhibitor liquid stream **296** to an impact zone **298** on the slide between the tissue sample **238** and the proximal end **100** of the slide, so that the tissue sample is not disturbed. The evaporation inhibitor liquid flows across the surface of the water layer on the wetted tissue, forming a thin evaporation inhibiting film **299** over the aqueous layer which usually covers most of the upper surface of the slide. The tissue is now ready for application of reagent.

The reagent delivery combination includes a conventional air cylinder **18** or equivalent actuator having an internal pressurized air activated piston. It is supplied with pressurized air by tubing **300**. Air cylinder **18** is supported by plate **216** and post **302** mounted on upper plate **8**. Delivery of pressurized air to the cylinder **18** causes rod **304** and its attached foot **306** to move downward against a reagent container **12** positioned in the reagent delivery zone. Downward movement of reagent container **12** causes emission of a precise volume of reagent liquid **310**. Suitable volumetric pumps are available from S. A. Valois and are described in U.S. Pat. No. 4,245,967 and French patent 2,528,122.

The reagent carousel support **314** is the drive plate which supports the reagent bottle carousel **10** and rotates it about its axis to place a predetermined reagent bottle **12** in the reagent delivery zone. An axially concentric circular array of low friction slide bearings **316**, mounted on the upper plate **8**, are positioned under the outer edge of the reagent support carousel.

The predetermined volume of aqueous reagent **310** impacts the evaporation inhibitor surface film between the impact zone **298** and the upper edge of the tissue sample **299**, passing through the film to the aqueous layer beneath the film and reaching the slide surface. The reagent then flows across the tissue sample **238** under the covering film of evaporation inhibiting liquid **299**. In this sequence, immediately after leaving the rinse stations, the slide is covered with the protective film to prevent any dehydration of the tissue sample **299**. The reagent solution is then applied to the protected tissue. Dehydration of the tissue section would irreversibly alter its physical and chemical characteristics and impair the immunohistochemical reactions. Dehydration is a constant hazard because of the constant flow of heated air over the slides required to maintain them at the desired temperature. The heated air temperature is determined by the requirements of the biochemical processes required by the process. It is slightly above 40° C., preferably about 45° C., for immunochemical reactions and can be as high as from 93 to 97° C. for in situ DNA hybridization reactions.

FIG. **15** also shows detailed elements of the heated air supply chamber **28** shown in FIG. **1**. Air is moved upward into the central intake manifold chamber **330** and through annular heating coils **331** and **332** mounted on annular air passageway plate **333**, to heat the air to a temperature slightly above 40° C., preferably about 45° C. A higher temperature can be provided as needed for in situ DNA hybridization procedures. The heated air passes through the outlet manifold chamber **334** and out the outlet passageways **336** in the lower plate **338**. Annular, axially concentric inner and outer heated air flow control curtains **340** and **342** direct the heated air downward over the slide surface. The reagent **310** falls through manifold passageway **344** to the slide surface.

The air temperature is monitored by heat sensor **345** positioned in the path of the heated air. A preferred heat sensor is a thermistor encased in a heat sensitivity adjusting jacket **347** which reduces the sensitivity of the thermocouple and approximates the thermal mass of the slides.

A reagent bar code reader **346** can be mounted on post **302**, positioned to scan a reagent bar code **348** on the reagent bottle **12**. Bar code **348** identifies the contents of the reagent bottle. At the beginning of a slide treatment operation, the reagent carousel **10** is rotated past the bar code reader **346**, and the bar code **348** on each reagent bottle **12** is scanned. The scanned information is fed to the computer and correlated with the indexed position of the reagent carousel **10**. This information is used to rotate the reagent carousel **10** to place the correct reagent bottle **12** in the application zone for each slide treatment step for each slide.

FIG. **16** is a cross-sectional view of one embodiment of the vortex mixing assembly, taken along the line C—C in FIG. **11**. Outer vortex jet block **222**, mounted on plate **22**, has an pressurized air supply channel **350** and nozzle **351**. Nozzle hanger **352** is mounted on the top of vortex block **22** and supports suspended inner vortex air jet nozzle block **224**. Channel **354** supplies nozzle **355** in block **224** with pressurized air. Nozzles **351** and **355** have central axes which form angles 'd' and 'e' of from 5 to 15° with the horizontal, directing air jets **356** and **357** toward the slide surface at the corresponding acute angles.

FIG. **17** is a top schematic view of the vortex mixing zone, showing details of the vortex mixing action. Pressurized air is supplied to the nozzle channels **350** and **354** by channel **358**. The reagent solution covered by a layer **360** of evaporation inhibiting liquid **360** is stirred on the surface of the biological sample by applying at least one gas stream **356** or **357** to an area of the surface of the evaporation inhibiting liquid layer **360** between the center of the evaporation inhibiting layer **360** and the edge of the planar support surface **361** or **362** of the slide **228**. The gas stream impacts the surface of the evaporation liquid surface layer **360** and moves the underlying reagent solution in a circular path on the tissue section. Preferably, the reagent solution is stirred on the surface of the biological sample by a vortex formed by applying two gas streams **356** and **347**. Stream **356** is directed against a area **363** of the surface of the evaporation inhibiting liquid layer between the center of the evaporation

inhibiting layer and the slide edge **361**. Stream **357**, in a direction opposite to the direction of stream **356**, is directed against an area **364** of the surface of the evaporation inhibiting liquid layer between the center of the evaporation inhibiting layer and the slide edge **362**. Although this method is shown with respect to an evaporation liquid inhibitor covered reagent layer, it will be readily evident that it can be applied to gently stir any liquid layer overlying a fragile substance.

FIG. **18** is a schematic representational cross-sectional view of a slide **370** following the rinse liquid, evaporation inhibitor and reagent application steps. Following the rinse stages (Stage A), the tissue section **371** mounted on slide **370** is covered with a thin residual aqueous layer **372**. Following application of the evaporation inhibitor liquid (Stage B), the aqueous layer **372** and tissue section **371** is entirely covered by a layer **373** of the evaporation inhibitor liquid. Aqueous reagent **374**, applied to the slide, flows under the evaporation inhibitor layer **373** to cover the tissue section. In the vortex mixing section (Stage C), air jets directed against the surface of the evaporation inhibitor liquid **373** move it and the reagent solution **374** thereunder in a swirling or stirring action on the surface of the fragile tissue section. This gentle stirring achieves increased interaction of reagent with the tissue section while preserving the tissue from dehydration or other damage from the air jets.

FIG. **19**A is a cross-sectional view of one embodiment of a rinse liquid container and associated heating components. The rinse liquid applied to the surface of the slides by rinse blocks **200**, **202** and **204** should have a temperature above 40° C. and is preferably about 45° C. The elevated temperature is critical for the immunochemical reactions. The rinse liquid is supplied by the hot water supply **44**. The hot water supply **44** comprises an inner container of an inert material having a low coefficient of expansion such as a pyrex bottle **382** having a threaded neck **384** to which a cap **386** is attached by threads. The container **382** is surrounded by an insulating jacket **388** of suitable insulation material such as a fiberglass layer. Between the insulating jacket **388** and the bottle **382** is a heating jacket **390** with electrical power leads **392**. A suitable heating jacket is a thick sheet of silastic rubber (polysiloxane) with embedded resistance heating coils having a combined heating value of about 180 watts. A conventional safety thermostat **394**, connected to the elements of the heating jacket, is also provided between the insulating jacket **388** and bottle **382**. The safety thermostat prevents the rinse liquid temperature from exceeding a preset value, preferably about 50° C. A thermistor temperature sensor **391** with leads **393** extends through the cap **386** into the upper zone of the bottle **382**. An liquid inlet tube **394** extends through the cap **386** to the bottom of the neck **384**, and an outlet tube **396** extends through the cap **386** to the bottom of the bottle **382**.

This unique configuration provides a highly uniform liquid output temperature. The colder water entering through the inlet tube **394**, being more dense than the heated liquid in the bottle, sinks downward past the heated container walls and is heated. The displaced liquid rises upward in the container. This stirring motion thoroughly mixes the liquid without the need for an agitator, producing a highly uniform outlet liquid temperature. Thermistor **391** constantly monitors the liquid temperature, providing a signal to the control system which is used to determine when the heating elements in jacket **390** should be energized.

FIG. **19**B illustrates an alternative embodiment of the rinse liquid container and associated heating components of the present which is similar to the structure illustrated by FIG. **19**A except that the inlet tube **394** of the embodiment of FIG. **19** functions as an outlet tube **394**A and outlet tube **396** of the embodiment of FIG. **19** functions as an inlet tube **396**A, i.e., the inlet and outlet lines have been reversed. This arrangement prevents the build up of air or gas in the bottle **384**. Additionally, the inlet tube **396**A has been provided with perforations **396**B for obtaining mixing as the bottle **384** is replenished with liquid.

FIG. **20**A is a bottom, isometric view of one embodiment of a reagent container support carousel **10**. According to this embodiment, the reagent container carousel **10** has feet **800**, **801** and **802** which rest in respective matching recesses in the reagent carousel support **314** (FIG. **15**) in only one position. This insures that the reagent carousel **10**A and the reagent bottle receptors **11** are always positioned in predetermined orientation on the carousel support **314**.

The feet **800**, **801** and **802** also function as supporting feet when the reagent support carousel **10** is removed. Refrigeration of the reagents is often required during their storage. The reagent container carousel **10**, with the reagent bottles supported thereon, can be lifted from the carousel support **314** and placed in a refrigerator, supported by the feet **800**, **801** and **802**.

Indexing metal homing block **803** is mounted on the reagent container carousel **10** and rotates with the carousel **10**. A conventional metal proximity detector (not shown) is mounted on the upper plate **8** at an position which places it adjacent the rotational path of the homing block. A change in electrical signal from the proximity detector indicates that the metal homing block is in the 'home' position adjacent the block.

FIG. **20**B is an alternative embodiment of a reagent support carousel **10**A and associated carousel support **314**A wherein a handle **804** has been provided to assist in the removal and replacement of the reagent support carousel **10**A as described above. In this embodiment, the carousel **10**A is provided with a plurality of feet **800**A, for example, five feet, which are substantially cylindrical elements with beveled edges **805**, and fit into corresponding and matching circular openings **802**A, formed in the associated carousel support **314**A. The feet **800**A and opening **802**A are positioned so that the carousel **10**A will fit into the support **314**A in only one position such that the carousel **10**A is always positioned in a predetermined orientation on the support **314**A. The support **314**A is provided with a central hub **806** which is received in a central opening **807** formed in the carousel **10**A, the hub being provided with beveled edges **808**. Engagement of the carousel **10**A and the support **314**A is best seen in FIG. **20**C. Except for the above described differences, the carousel **10**A and the support **314**A are the same as previously described.

FIG. **21** is a fragmentary cross-sectional view taken along the line D—D in FIG. **11**. Indexing block **229** is a metal block. Proximity sensor **610** is supported on the underside of plate **22** by bracket **611**. The proximity sensor **610** emits an electrical signal through leads **612** which changes when the metal block **229** is positioned in the 'home' position immediately above the sensor.

The homing systems of the reagent carousel **10** and slide support carousel **24** operate in a similar manner. Presence of an indexing block adjacent the sensor produces a signal indicating that the carousel is in a "home" position, and provides a reference for subsequent indexed movements of the respective stepper motor drive and subsequent indexed movements of the respective carousel.

FIG. **22** is a schematic view of the pneumatic system of the automated immunostaining apparatus of this invention.

The air supply for the system is supplied by air compressor **80** and air filter **82**. The output line **400** from the air filter **82** is connected to the input port of air pressure regulator **86** where it is regulated to a constant output pressure of about 25 psi. Diaphragm pressure switch **402** communicates with the air pressure regulator **86** outlet line **403** through line **404**. Diaphragm pressure switch **402** closes the system circuit breaker **406** when the pressure in line **404** is at least 22 psi. Failure of the air compressor and resulting drop in line pressure automatically deactivates the system.

The air output branch line **408** lead is connected by line **410** with tipper air cylinder three way control solenoid valve **412**. When in an "open" position, solenoid valve **412** provides communication between input line and cylinder **278**. This permits pressurized air to pass from line **410** to air cylinder **278**, thus pressing tipper tip **148** (FIG. **14**) against the respective slide support tab **112** and tipping the slide support **206**. When solenoid valve **412** returns to the vent position, the air cylinder **278** communicates with atmosphere, permitting the air cylinder **278** to return to its resting position. Tipper tip **148** then rises to its resting position, allowing the slide support to also return to its horizontal position. Three way solenoid valves **416** and **420** operate in an identical way, providing communication between the air inlet lines **414** and **418** and the respective air cylinders **280** and **282** when in the open position and actuating respective tipper tips **284** and **286**. They also open communication between the air cylinders **280** and **282** and the atmosphere in the vent position, allowing the tipper tips to return to their elevated position.

Branch line **422** leads from line **408** to the reagent dispenser three way control solenoid valve **424**. When energized to an "open" position, solenoid valve **424** permits pressurized air to pass from line **422** to air cylinder input line **300**, causing rod **302** and foot **306** (FIG. **15**) to press the reagent dispenser bottle **12** downward, emitting a precise volume of reagent liquid. When solenoid valve **424** is in the vent position, the air cylinder **18** and the reagent bottle **12** return to their resting positions.

Branch line **426** leads from line **403** to branched lines **428** and **430**. Branch line **428** leads to pressure regulator **38**, providing an output pressure of **10** psi in output line **431**. Three way solenoid valve **432**, when in the open position, provides communication between air input line **431** to the evaporation inhibitor liquid reservoir container **434** through lines **436** and **438**. It also delivers pressurized air to the rinse liquid supply container **44** through line **440**, rinse solution reservoir **441** and supply conduit **443**. When solenoid valve is opened to atmosphere (vent position), air in line **436** and in containers **44** and **434** is bled or vented to the atmosphere. This permits removal, opening or replacement of reservoir container **434**, or opening or removal of supply container **441**. The pressured air in containers **434** and **441** forces liquid through respective output conduits **442** and **443**.

Conduit **442** leads to two way solenoid valve **446**, which has an outlet conduit **448** leading to the evaporation inhibitor application block **212** and associated nozzles. When the solenoid **446** is opened, evaporation inhibitor liquid is emitted from nozzles **294** (FIGS. **14** and **15**) onto the surface of the respective slide **234**.

Conduit **444** delivers pressurized rinse liquid from heated rinse liquid container **44** to branch conduits **450**, **452** and **454** leading to conventional rinse liquid two way solenoid valves **460**, **462** and **464**. When the solenoid valves **460**, **462** and **464** are opened, pressurized rinse liquid is delivered to the respective rinse blocks **200**, **202** and **204** through supply conduits **260**, **268** and **276**. The pressurized rinse liquid is emitted by the rinse blocks onto the slides positioned in the respective station (FIG. **13**).

Branch line **430** leads to pressure regulator **64**, providing an output pressure of 15 psi in output conduit **466** leading to vortex mixer air control two way solenoid valve **468**. When in the open position solenoid valve **468** delivers pressurized air to output conduit **470** connected thereto. Conduit **470** leads to branch lines **472** and **474** leading to vortex mixing blocks **222** and **224**. The pressurized air is emitted by nozzles **351** and **355** (FIG. **17**), stirring the reagent layer on the respective slides **234**.

FIG. **23** is a schematic drawing of the 120 volt AC power distribution in the apparatus of this invention. The power circuit to power line filter **500** includes a main fuse **504** and main power switch **506**. 120 Volt AC power to the air compressor **80** is provided by line **511** from the line fuse **510** in the I/O board **508**. 120 Volt AC power to the air compressor cooling fan **514** is provided by line **513** from line fuse **512** in the I/O board **508**. 120 Volt AC power to the electronics cooling fan **518** is provided by line **517** from line fuse **516** in the I/O board **508**. 120 Volt AC power to the 24 volt DC power supply is provided by line **521** from line fuse **520** in the I/O board **508**. 120 Volt AC power to the 5 volt/12 volt DC power supply **78** is provided by line **524** from line fuse **522** in the I/O board **508**. 120 Volt AC power to the computer card rack **529** is provided by line **528** from line fuse **526** in the I/O board **508**. 120 Volt AC power to slide heater fan relay **533** is provided by line **532** from line fuse **530** in the I/O board **508**. 120 Volt AC power to the slide heater relays **537** is provided by line **536** from fuse **534** in the I/O board **508**. 120 Volt AC power to the rinse fluid heater relay **541** is provided by line **540** from fuse **538**.

FIG. **24** is a schematic drawing of the DC power distribution in the apparatus of this invention. 12 Volt DC logic power for printer **550** is provided by line **552** from the power supply **78**. Similarly, 12 volt DC power for low slide temperature controller **68** is provided by line **554**, 12 volt power for high slide temperature controller **70** is provided by line **556**, and 12 volt power for rinse fluid temperature controller **66** is provided by line **558**. 5 Volt DC laser power for the slide bar code reader **231** is provided by line **560** from the power supply **78**, and 5 volt power for the laser of reagent bar code reader **346** is provided by line **562**. 5 Volt DC power to the liquid crystal display **34** is provided by line **564**.

24 Volt DC power is provided to the upper motor controller **566** for the stepper motor **14** by line **568**. 24 Volt DC power for the lower motor controller **570** for the stepper motor **48** is provided from power supply **76** by line **572**.

The conventional card rack **529** has a separate 5 volt/12 volt power supply **576**. 5 Volt DC logic power and 12 volt DC motor power is provided to the floppy disc drive by lines **574**.

FIG. **25** is a schematic drawing of a first portion of the computer digital I/O system in the apparatus of this invention. The control system uses a series of standard optical relays, each of which are connected to close the line to ground in the power circuit for the respective component. The optical relays provide isolation.

Communication between the optical relays and the computer digital I/O board **580** is provided by lines **582**. The two way solenoid valves **460**, **462** and **464** controlling the rinse liquid flow from heated rinse supply **44** to the respective rinse blocks **200**, **202** and **204** are energized to an open position and de-energized to a closed position by output

signals from the computer digital I/O board **580** to the optical relays **584**, **586** and **588**. The two way solenoid valve **446** controlling the flow of evaporation control liquid from container **434** to the nozzle block **212** is energized to an open position or de-energized to a closed position by output signals from board **580** to optical relay **590**.

The three way solenoid valves **412**, **416** and **420** controlling air flow to the respective tipper air cylinders **278**, **280** and **282** are energized to an open position (causing air flow) or de-energized to a closed position (venting cylinder air to the atmosphere) by output signals from computer I/O board **580** to respective optical relays **592**, **594** and **596**. The three way solenoid valve **424** controlling air flow to the micro delivery reagent dispenser control cylinder **300** is energized to an open position (causing air flow and reagent delivery) or de-energized to a closed position (venting cylinder air to the atmosphere) by output signals from computer I/O board **580** to respective optical relay **598**. The two way solenoid valve **468** controlling air flow to the vortex air mixer blocks **220**, **222** and **224** (FIG. **17**) is energized to an open position (causing air flow to the mixer blocks) or de-energized to a closed position by output signals from computer I/O board **580** to respective optical relay **600**.

The sound alarm **602** is activated to produce sound by an output signal from the computer I/O board **580** to optical relay **604**. The sound alarm **602** can be activated to sound a 'beep' by keyboard key operation, by a longer 'beep' or double 'beep' at the completion of a run, and a sustained sound during a system malfunction, for example. The three way solenoid valve **432** controlling air flow to the rinse liquid and evaporation control liquid supply containers **44** and **434** (FIG. **22**) is energized to an open position (causing air flow and pressurization of the supply containers) or de-energized to a closed position (venting cylinder air from the containers to the atmosphere) by output signals from computer I/O board **580** to respective optical relay **606**.

The slide heat fan **56** speed is operated by pulse width modulation, that is, power pulses from the power relay **608**. The fan **56** is energized by an output signal to the power relay **608** from optical relay **610**. The timed signal to the optical relay **610** is received from the computer I/O board **580**. The pulse width and speed of the fan **56** is adjusted in response to heating requests from the high temperature slide controller **632** to increase the volume of heating air delivered to the air distribution manifold **30**.

The slide heater system control supplies separately controlled power to each of the resistance heating elements **331** and **332**. Low temperature heating element **332** is energized by power relay **612** upon a signal from the low slide temperature controller **614**. Thermistor **347** provides temperature information to the controller **614**. During the operation of the apparatus at the lower temperatures required for the immunohistological processes, the power to the heating element **332** is turned on when operating heat is required, in response to a low temperature signal from the low temperature controller **614**. It is turned off when the operating temperature is restored. The controller **614** also detects when the slide door switch **616** is closed. If the cabinet slide door is open, energy supply to the heating element **331** and **332** is interrupted. The heating cycle is initiated by a request for heat passed to the computer I/O board **580** through line **624** to the optical relay **622**. The computer then responds with a heating power select heat signal received by controller **614** through line **620** from optical relay **618** in response to an output signal from the computer I/O board **580**. A status signal for the slide door switch is received by the computer I/O board through line **628** and optical relay **626**.

The high temperature heating element **331** is energized by power relay **630** upon a signal from the high slide temperature controller **632**, in response to a power command signal through optical relay **634** and line **636** from the computer digital I/O board **580**. During the operation of the apparatus at the lower temperatures required for the immunohistological processes, the power to the heating element **331** is turned on only during an initial warm-up cycle. During the warm-up cycle, heat energy is requested from the I/O board **580** through line **638** and optical relay **640**.

When the apparatus is operated at the higher temperatures required for in situ hybridization, the heating elements are energized in a different control sequence by the controllers **614** and **632**. As with the low temperature operation, both heating elements **331** and **332** are energized during the warm-up cycle. However, in the high temperature operating mode, the low temperature heating element **332** is continuously energized, and energy is supplied intermittently to the heating element **331**. In the high temperature mode, therefore, the optical relay **634** receives a power command signal from the I/O output board **580** when the high temperature controller **632** signals that more heat is required. In addition to the heater controls described above, an additional thermostat is provided in the heater circuit which turns the heater off if the heater temperature reaches 160° C., for example if the fan **56** fails.

The rinse liquid heating system resistance heater **390** (FIG. **19**) is energized through power relay **642** upon a signal from rinse fluid controller **644**. Thermistor **391** monitors the rinse fluid temperature, and the controller **644** provides a signal indicating whether or not further heat energy is required. A heat request signal for heating liquid is received by the computer I/O board through line **646** and optical relay **648**. The computer responds with a heat select signal from the I/O board **680** through relay **650** and line **652**.

FIG. **26** is a schematic drawing of a second portion of the computer digital I/O system in the apparatus of this invention. The computer digital I/O board **580** receives a signal indicating closure of the air pressure switch **402** (FIG. **22**) through line **670** and optical relay **672**. The computer digital I/O board **580** receives a home signal from the reagent carousel metal proximity home sensor through line **676** and optical relay **674** when the metal block **803** and the reagent carousel **10** are in the home position. The computer digital I/O board **580** receives a home signal from the slide support metal proximity home sensor **610** through line **680** and optical relay **678** when the metal block **229** and the slide support carousel **24** are in the home position.

The reagent carousel stepper motor **14** is operated by reagent carousel stepper motor controller **690** in response to commands received from the computer digital I/O board **580**. Command signals for steps (motor operation) are received through line **692**, and command signals for the direction of operation are received through line **694**. The stepper motor has a high and low torque operating mode, the low torque mode being effected by switching a resistor into the control circuit. The high torque mode is used to move the motor through the number of steps required to place a selected reagent bottle in the reagent delivery station. The low torque mode is used as a brake to hold the reagent bottle carousel in a position. The low or high torque command signal is received by the reagent carousel stepper motor controller **690** through line **698** and optical relay **696**.

The slide support carousel stepper motor **48** is operated by slide support carousel stepper motor controller **700** in response to commands received from the computer digital

I/O board **580**. Command signals for steps (motor operation) are received through line **702**, and command signals for the direction of operation are received through line **704**. This stepper motor also has a high and low torque operating mode, activated in the same way and having the same functions as the reagent carousel stepper motor operating modes. The high torque mode is used to move the motor through the number of steps required to place a selected slide in a selected treatment zone. The low or high torque command signal is received by the slide support carousel stepper motor controller **700** through line **708** and optical relay **706**. When the door switch **616** shows an open door status, the step command signals to the stepper motors **14** and **48** are prevented. If the door switch **616** is opened during a biological processing run, any incomplete stepper motor sequence is permitted to reach completion before further step command signals are blocked.

The keyboard **710** is a conventional pressure sensitive keyboard. The switches **720–726**, **730–736**, **740–746** and **750–756** are closed by manual pressure applied to the surface of an impermeable flexible plastic layer over the switches. The switches are isolated and protected under the plastic layer and are not fouled by moisture or debris from the laboratory or operator.

In operation input lines **711**, **712**, **714** and **716** are each sequentially energized for a brief period by the computer digital I/O board **580**, and the lines **718**, **728**, **738** and **740** are each sequentially polled during this brief period. If line **718** polls positive while line **716** is energized, closure of switch **720** is indicated. In a similar manner, closure of switch **722** is indicated by a positive poll of line **718** when line **714** is energized, closure of switch **724** is indicated by a positive poll of line **718** when line **712** is energized, closure of switch **726** is indicated by a positive poll of line **718** when line **711** is energized, and the like.

FIG. **27** is schematic drawing of the computer serial and floppy disk I/O system in the apparatus of this invention. The computer RS-232 I/O port **770** sends polling signal to the slide barcode reader **231** and receives signals indicating bar code information read through line **772**. Similarly, the computer RS-232 I/O port **770** sends polling signal to the reagent carousel barcode reader **346** and receives signals indicating barcode information read through line **774**. Signals to the liquid crystal display **34** are sent through line **776** from the RS-232 I/O port **770**. The computer RS-232 I/O port **770** receives an availability polling signal from the printer **550** and sends digital data to printer **550** through line **778**.

Immunohistological methods for which the apparatus of this invention are particularly suitable are described in concurrently filed, commonly assigned patent application Ser. No. 07/488,601, filed Mar. 2, 1990, now abandoned, the entire contents of which are hereby incorporated by reference. A typical immunohistological method, as carried out with the apparatus of this invention includes the following steps.

1) Preparing the slides, including applying a bar code to the slide indicating the immunohistological process to be used with the sample, and manually rinsing and applying evaporation inhibiting liquid to the tissue sample surface before placement in the apparatus to prevent dehydration of the sample.

2) Inserting a batch of slides in the apparatus, mounting each slide in a slide support.

3) Closing the apparatus and beginning the treatment processing. The apparatus heating system is in the warm-up mode until the heating air temperature reaches the desired level.

4) A slide is rinsed in the first rinse station (FIGS. **11–14**) in seven rinse cycles. Each cycle includes applying a 500 μL pulse of rinse liquid followed by tipping the slide support to effect draining. This sequence can be repeated for seven rinse cycles as the slide is moved to and pauses in each of the second and third rinse stations, for a total of twenty-one rinse cycles, for example. The slide then is treated in a seven second stay in the evaporation inhibitor and reagent solution application station (FIGS. **11**, **14** and **15**). An initial quantity of 500 μL of an evaporation inhibiting liquid such as dodecane is applied to the slide surface. Then 200 μL of reagent solution is applied to the slide.

As each slide poises in the reagent application zone, the appropriate reagent container is moved by the reagent carousel to the reagent application station, and a metered volume of reagent is applied to the slide. In being applied to the slide, the reagent liquid is applied to the uppermost surface (the evaporation liquid layer). It then passes through the evaporation inhibiting liquid layer to the underlying aqueous layer, a procedure which would not be possible with a conventional solid glass coverslip.

6) The slide is then passed to each of the vortex mixing stations (FIGS. **11**, **14**, **16** and **17**). Here vortex jets stir the reagent on the slide surface under the file of evaporation inhibiting liquid. This procedure would not be possible with a conventional solid glass coverslip.

7) The slide is then carried by the carousel, pausing as each slide support is sequenced through the same steps, until it returns to the initial rinse station, where the cycle is repeated. The reaction between the reagent and the tissue sample continues during this period, and slides in each of the following slide supports is subjected to the same sequence of rinse, application of evaporation inhibitor, application of reagent, stirring, and incubation.

8) In a typical immunohistological process using a four phase process with a peroxidase enzyme antibody label, a sequence total of five different reagents are applied as the tissue sample is passed five times through the reagent application zone. In such a process, the first reagent is a hydrogen peroxide solution required to eliminate endogenous peroxidase activity in the tissue sample. The second reagent is a primary antibody which binds selectively with an specific epitope for which the sample is being tested. The third reagent is a biotin labeled secondary antibody which binds preferentially with the primary antibody remaining on the sample following the preceding incubation and rinsing. The fourth reagent is avidin labeled with an enzyme such as a peroxidase enzyme, the avidin binding with the biotin label remaining on the sample following the preceding incubation and rinsing. The fifth reagent is a substrate solution which is converted by the peroxidase enzyme to form a detectable label such as a fluorophore or chromophore at the site of any primary antibody binding with the sample.

9) Following the conclusion of the substrate solution treatment and incubation, the slide typically is removed from the carousel, coverslipped with a glass coverslip and examined to determine the extent of primary antibody binding with the tissue sample.

FIG. **28** illustrates an alternative embodiment of the intermediate section **4**, including the slide support carousel

24 and the associated slide treatment stations, which dispenses with the tipper rinse method described above and employs an alternative rinsing arrangement, using stationary slide supports, as will be more fully described hereinafter. The carousel **24** is rotated, for example, in a clockwise manner, as indicated by the arrow shown in FIG. **28**, so that each slide support **26**A and associated slide **234** is positioned in the rinse zone A, evaporator inhibitor and reagent application zone B, and agitation zone C for successive treatment and incubation as previously described above.

In the embodiment depicted by FIG. **28**, an alterative embodiment of the slide support **26**A is provided which does not pivot, but rather is fixedly supported in a predetermined position on the carousel **24** by screws or the like and structured so that the associated slide **234** is held substantially horizontally as best seen in FIGS. **29**A–29B. Referring to FIGS. **29**A–**29**B, the slide support **26**A has a distal end **103**A, which is juxtaposed to the center of the carousel **24**, and a proximal end **104**, which is positioned adjacent to an outer circumference of the carousel **24**.

The support **26**A comprises a support plate **102**A having a raised terminal guide end platform **106**, adjacent the proximal end **104**A and a support post **107**A, adjacent the distal end **103**A. The platform **106**A and the post **107**A cooperate to support the slide **234** in a substantially horizontal position at a predetermined vertical distance with respect to raised terminal guide tabs **108**A and **109**A between which the slide **234** is positioned.

As best seen in FIG. **29**B, the tabs **108**A, **109**A are provided with a vertical length such that the upper surface of the slide **234** is positioned above the upper ends of the guide tabs **108**A, **109**A while the respective lateral edges **111**A, **113**A of the tabs **108**A, **109**A engage the lateral sides of the slide **234**, i.e., the tabs **108**A and **109**A do not extend a far as the upper surface of the slide **234** to prevent wicking-off of any liquid on the upper surface of the slide **234** by the tabs **108**A and **109**A. The lateral edges **111**A, **113**A cooperate with the a guide edge **115**A at the platform **106**A to orient the slide **234** at a predetermined position with respect to the slide support **26**A, and thus the carousel **24**, for treatment at the various treatment stations to be describe hereinafter.

A clamping arrangement, generally indicated at **118**A, positioned at the proximal end **104**A, clamps the slide **234** to the slide support **26**A. The clamping arrangement comprises a pair of supports **119**A between which a slide engaging member **120**A is pivotally supported. Spring **121**A biases the slide engaging member **120**A to firmly hold the slide **234** against the platform **106**A and post **107**A. The slide support **26**A permits easy loading and unloading of the slide **234**, firmly holds the slide **234** in place, does not interfere with the operation of the bar code reader and prevents or minimizes the wicking, i.e., surface tension, from draining liquids off the slide **234**.

An alternative embodiment of the rinsing arrangement forming the rinse zone A is employed in the embodiment depicted by FIG. **28** which replaces the rinse blocks, and arrangement thereof, used with the tipper rinse method previously described with respect to FIG. **14**. Referring to FIG. **28**, the rinse zone A employs a first rinse block **200**A, having a single wash block nozzle, as best seen in FIGS. **30**A–**30**B, and a second rinse block **202**A, having a dual wash block nozzle, as best seen in FIG. **31**.

The first wash block **200**A is preferably positioned at the beginning of the rinse zone A and the second wash block **202**A is preferably positioned at the end of the rinse zone A so that the first and second wash blocks are spaced from one another. The first wash block **200**A pulses streams of rinse liquid onto a slide upon entering the rinse zone A and due to the meniscus effect of the rinse liquid at the edges of the slide, builds up a layer of rinse liquid which remains on the slide. After a predetermined waiting period, set by the time it takes for the slide carousel to transport a slide between the first and second wash blocks **200**A, **202**A, the second wash block **202**A uses pulsed streams of rinse liquid, alternately directed at one and then the other of the longitudinal edges of the slides, to knock or sweep the previously deposited layer of rinse liquid off of the slide.

The rinsing arrangement depicted in FIG. **28** rinses or washes the upper surface of the slides with streams or jets of pulsed rinsing liquid, for example, water, so that a low volume of rinsing liquid is used to provide a high degree of rinsing. Because the rinsing of the slides is a key limit to the sensitivity of the assays as background or noise is directly related to rinsing and sensitivity is the signal to noise, ratio, the wash blocks **200**A, **202**A precede the application of the reagent and are a preferred feature of this embodiment of the invention.

Referring to FIG. **30**A, the first wash block **200**A comprises a single wash block nozzle **201**A having a plurality of nozzle outlet openings **203**A, for example **10** or so openings, which each provide a pulsed stream of rinse liquid **204**A which impacts the rinse liquid impact zone **236** of the slide **234** as previously described. Due to the meniscus effect of the rinse liquid at the longitudinal edges **234**P and lateral edge **234**L of the slide **234**, a layer of rinse liquid **213**A is built up on the slide **234** as a result of the repeated pulsing of streams of rinse liquid during the operation of the first wash block **200**A.

As best seen in FIG. **30**B, a nozzle axis **240**A of the nozzles of block **200**A forms an angle b with the horizontal, this angle being between 15 and 35 degrees, preferably substantially 25 degrees.

FIG. **31** illustrates the second wash block **202**A which employs a dual wash block nozzle **205**A comprising a lower set of nozzle outlet openings **206**A and an upper set of nozzle outlet openings **207**A which respectively direct streams of pulsed rinse liquid towards one or the other of the longitudinal edges **234**P of the slide **234**.

As with the first wash block **200**A, the streams of pulsed rinsing liquid, from each of the lower and upper sets of nozzle outlet openings **206**A and **207**A, preferably impact the slide **234** at the rinse liquid impact zone **236** which is upstream on the slide **234** from the tissue sample (not shown) positioned thereon. This feature of the first and second wash blocks **200**A and **202**A is important due to the fragile nature of the tissue sample positioned on the slide **234**. By directing the streams of pulsed rinsing liquid at the impact zone **236** of the slide **234**, the rinse liquid is provided with laminar flow by the time the rinse liquid reaches the tissue sample. As a result, undue damage to the fragile tissue sample is prevented.

The upper set of nozzle outlet openings **207**A is constructed so that the associated streams of rinse liquid are off-set at an angle from the longitudinal center line of the slide **234** so that the pulsed streams of rinse liquid are directed toward one of the longitudinal edges **234**P of the slide **234**. The lower set of nozzle openings **206**A is constructed so that the associated streams of rinsing liquid are also off-set at an angle from the longitudinal center line of the slide **234** so that the pulsed streams of rinse liquid are directed toward the other one of the longitudinal edges **234**P of the slide **234**. As a result of this arrangement, pulsed streams of rinse liquid are alternately and repeatedly directed to one and then the other of the longitudinal edges **234**P of the slide **234** as will be more fully described hereinafter.

Preferably, separate plumbing and valving are provided for each of the lower and upper sets of nozzle outlet openings **206**A and **207**A of the dual wash block nozzle **205**A to permit independent operation thereof. In operation, wash block **202**A directs streams of pulsed rinsing liquid, for example from the lower set of nozzle openings **206**A, toward a single longitudinal edge **234**P of the slide **234** and after completion then directs streams of pulsed rinse liquid, for example from the upper set of nozzle opening **207**A, to the other longitudinal edge **234**P of the slide **234**. This procedure is repeated and has the effect of sweeping or knocking the layer of rinse liquid **213**A off of the slide **234**.

As with the first wash block **200**A, the nozzle axis **240** (not shown) of each of the upper and lower set of nozzle openings **207**A, **206**A forms an angle b (not shown) with the horizontal of between 15 and 35 degrees, preferably substantially 35 degrees for the upper set of openings **207**A and substantially 25 degrees for the lower set of openings **206**A.

FIG. **32** illustrates an alternative embodiment of a vortex air mixer **220**A which in this case is a single mixer. Each of the single vortex air mixers **220**A is positioned at the inner radius of the slides **234** such that an gas jet or cone **356**A of, for example, air or the like, blows outwardly adjacent one of the longitudinal lateral edges **234**P of the associated slide **234** to effect mixing in a manner similar to that described with respect to FIG. **17**. More specifically, the gas stream **356**A impacts the surface of the evaporation liquid surface layer **360** and moves the underlying reagent solution in a circular path on the tissue section.

Each vortex mixer **220**A has a nozzle channel **350**A, including a nozzle orifice **351**A, which is supplied with pressurized air via a supply channel **358**A, the nozzle channel **350**A preferably intersecting the supply channel at a lower portion thereof. Pressurized air is supplied to the supply channel **358**A from a air supply conduit **352**A (arrows indicating the flow of air to and from the mixer **220**A) connected to a pressurized air source (not shown). Each of the vortex mixers **220**A can be supplied with pressurized air via a common supply conduit **352**A which connects and supplies each of the supply channels **358**A of the plurality of mixers **220**A illustrated in FIG. **28**.

As best seen in FIG. **28**, there are, for example twelve, single vortex mixers **220**A on the inner radius of the slides **234**. The nozzle orifice **351**A of each of the mixers **220**A is preferable positioned so that the center of the gas net or cone **356**A is approximately 2 mm above the surface of the slide **234** and 4 mm in from the adjacent edge **234**X of the slide **234** as best seen in FIG. **32**.

A first mixer **220**A is preferably positioned at station S2 adjacent the reagent drop point station S1 and a second mixer **220**A is positioned at station S3, the mixers **220**A at stations S2 and S3 directing the stream of air **356**A to opposite longitudinal edges **234**P of an associated slide **234** so that mixing is enhanced as described below.

The exact positioning of the remaining mixers **220**A is not critical, these mixers **220**A being positioned to provide a semi-continuous mixing. Additionally, each mixer **220**A is spaced so that they alternate in blowing the right side and then the left side of the slide **234**. That is, the even mixers blow up the right side of each slide **234** passing by and the odd mixers blow up the left side or vice versa. This enhances kinetic mixing, provides uniform coverage and averages out any possible temperature differences across each of the slides **234**. These features lead to more rapid and reproducible staining than can be obtained manually.

Additionally, the intermediate section **4** of the embodiment of FIG. **28** is provided with a bar code cleaner, generally indicated at **233**A, for cleaning drops of liquid off of the bar codes **233** (FIG. **32**) provided for each of the slides **234** for identification purpose as previously described. It should be noted that the bar code cleaner **233**A is equally applicable to the previously described embodiment of the invention employing the tipper rinse method described above. The bar code cleaner **233**A is positioned, for example, downstream from the reagent drop point station S1 just beyond the first vortex agitation zone C as best seen in FIG. **28** and upstream and adjacent to the bar code reader position (not shown).

The bar code cleaner **223**A is illustrated in detail in FIGS. **33**A–**33**B and comprises a bar code nozzle **333**A supplied with compressed air or the like via a supply channel **334**A which is connected to a compressed air source (not shown) by supply conduit **335**A. The bar code nozzle **333**A is supported above the slide carousel **24** by support **336**A, as best seen in FIG. **33**B, and affixed to the stationary support plate **22** of the intermediate section **4**. The nozzle **333**A emits a stream or cone of air **337**A which blows across the bar code **233** of an adjacent slide **234** attached to the associated slide support **26**A. The stream of air **337**A blows drops of liquid off of the bar code **233** which otherwise interfere with the reading of the bar codes by the bar code reader.

As best seen in FIG. **33**A, the nozzle axis **338**A of the bar code nozzle **333**A forms an angle of about 45 degrees with the horizontal. Additionally, the stream of air **337**A preferably strikes the bar code **233**A in the area of the side of the bar code **233**A closest to nozzle **333**A.

Since the embodiment of the intermediate section **4** described with reference to FIG. **28** does not employ the tipper rinse method, any rinse liquid remaining on the slide after operation of the second wash block **202**A is drained from the upper surface of the slides **234** by a jet drain **148**A which is illustrated schematically by FIG. **34**. The preferred position of the jet drain **148**A is at the last rinse station of the rinse zone A just prior to the reagent drop point station S1 as best seen in FIG. **28**.

The jet drain **148**A directs a fluid stream **150**A of, for example air, at substantially a 45 degree angle to the longitudinal axis of an associated slide **234** and across one corner of the distal end **104**A of the associated slide **234**. The action of the fluid stream **150**A acts to blow, aspirate or siphon the buffer remaining after the rinsing performed at the rinse zone A as described above.

Except for the differences noted above the embodiment so described with respect to FIG. **28** is the same as the apparatus described above in connection with the tipper rinse method and is capable of operating and performing the immunohistological methods as previously described.

What is claimed is:

1. A method of dispensing reagents onto a slide, the method comprising the steps of:

providing at least one reagent container;

providing at least one slide on a slide support;

automatically identifying the reagent container using a computer;

automatically determining whether reagent in the reagent container should be dispensed onto the slide; and

dispensing the reagent in the reagent container onto the slide based on the determination of whether the reagent in the reagent container should be dispensed onto the slide,

wherein the step of automatically determining whether reagent in the reagent container should be dispensed onto the slide includes the steps of:

providing a bar code reader;

reading a slide bar code placed on the slide using the bar code reader thereby acquiring slide information, the slide information indicating reagents to be applied to the slide; and

sending the slide information to the computer.

2. The method of claim **1** wherein the slide bar code identifies a slide sample placed on the slide and identifies a sequence of reagents for the slide sample.

3. The method of claim **1** further comprising the steps of:

determining position information for the slide; and

sending the position information to the computer.

4. The method of claim **3** wherein a slide support supports the slide and wherein the step of determining position information for the slide includes homing the slide support and determining an indexed position of a motor drive for the slide.

5. A method of dispensing reagents onto a slide, the method comprising the steps of:

providing a plurality of reagent containers in a reagent support, each of the reagent containers having a reagent barcode;

providing at least one slide on a slide support, the slide having a bar code;

providing a bar code reader;

reading the bar codes on the reagent containers;

determining reagents in the reagent containers based upon the reading of the bar codes on the reagent containers;

reading the slide bar code on the at least one slide;

determining a sequence of reagents to be applied on the at least one slide based upon the reading of the slide bar code on the slide; and

dispensing the reagents in the reagent containers based upon the sequence of reagents to be applied.

6. The method of claim **5** further comprising the steps of:

determining position information for the reagent containers; and

sending the position information to the computer.

7. The method of claim **6** wherein a reagent carousel supports the reagent containers and wherein the step of determining position information for the reagent containers includes homing the reagent carousel and determining an indexed position of a motor drive for the reagent containers.

8. The method of claim **5** further comprising the steps of:

determining position information for the at least one slide; and

sending the position information to the computer.

9. The method of claim **8** wherein a slide carousel supports the at least one slide and wherein the step of determining position information for the at least one slide includes homing the slide carousel and determining an indexed position of a motor drive for the at least one slide.

10. The method of claim **5** further comprising the step of moving the reagent containers and the slide support relative to one another based upon the sequence of reagents to be applied on the at least one slide.

11. An automated biological staining apparatus comprising:

a slide support for holding at least one slide;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

bar code reader;

reagent dispensing device for applying reagent onto a particular slide; and

computer in communication with the slide support drive means, the reagent drive means, bar code reader and means for dispensing reagent,

wherein the bar code reader reads reagent bar codes on the reagent containers and at least one slide bar code on the at least one slide, and

wherein the computer automatically determines whether reagent in the reagent containers should be dispensed onto the particular slide.

12. The automated biological staining apparatus of claim **11** further comprising:

homing device connected to the reagent tray and in communication with the computer wherein the homing device determines position information for the reagent containers.

13. The automated biological staining apparatus of claim **12** wherein the reagent drive means is a motor and wherein the homing device determines an indexed position of the motor for the reagent containers.

14. The automated biological staining apparatus of claim **12** wherein the reagent drive means is a motor and wherein the motor rotates the reagent tray so that the reagent bar codes on the reagent containers are read by the bar code reader.

15. The automated biological staining apparatus of claim **11** wherein the bar code reader reads the at least one slide bar code on the at least one slide and wherein the at least one slide bar code is sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the particular slide.

16. The automated biological staining apparatus of claim **11** further comprising:

homing device connected to the slide support and in communication with the computer wherein the homing device determines position information for the particular slide.

17. The automated biological staining apparatus of claim **11** wherein the computer controls the movement of the reagent tray and the slide support to move relative to one another to position a reagent container over the particular slide.

18. The automated biological staining apparatus of claim **12** wherein the reagent tray is a reagent carousel and wherein the reagent drive means moves the reagent carousel to place the reagent containers in a reagent delivery zone.

19. An automated biological staining apparatus comprising:

a slide support for holding at least one slide;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

means for automatically identifying the reagent containers;

means for automatically determining whether reagent in the reagent containers should be dispensed onto a particular slide; and

reagent dispensing device for applying reagent onto a particular slide.

20. The automated biological staining apparatus of claim **19** wherein the means for automatically identifying the reagent containers includes a bar code reader, wherein the bar code reader reads reagent bar codes on the reagent containers and wherein the reagent bar codes are sent to the computer for automatically identifying the reagent containers.

21. The automated biological staining apparatus of claim 19 wherein means for automatically determining whether reagent in the reagent containers should be dispensed onto the slide includes a bar code reader, wherein the bar code reader reads slide bar codes on the slides and wherein the slide bar codes are sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the particular slide.

22. The automated biological staining apparatus of claim 19 further comprising:

means for determining position information for the reagent containers, the means being in communication with the computer.

23. The automated biological staining apparatus of claim 22 wherein the means for determining position information for the reagent containers includes a homing device connected to the reagent tray and in communication with the computer wherein the homing device determines position information for the reagent containers.

24. The automated biological staining apparatus of claim 19 further comprising:

means for determining position information for the at least one slide, the means being in communication with the computer.

25. The automated biological staining apparatus of claim 24 wherein the means for determining position information for the at least one slide includes a homing device connected to the slide support and in communication with the computer wherein the homing device determines position information for the at least one slide.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Keith G. Copeland, et al.

Assignee: Ventana Medical Systems, Inc.

Title: "AUTOMATED BIOLOGICAL REACTION APPARATUS"

Serial No.: 07/924,052 Filed: 08/31/92

Examiner: Carpenter, R. Group Art Unit: 1801

Attorney Docket No.: M-1665-1P US

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5/23/94

San Jose, California
April 29, 1994

COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

AMENDMENT

Sir:

In response to the Office Action dated November 29, 1993 please amend the above-identified patent application as follows:

IN THE SPECIFICATION

At page 18, line 18, at the end of line 18 change "25" to --26--.

At page 19, line 33, between the words "in" and "showing" change "Fig. 10" to --Fig. 11--.

At page 28, line 28, between the words "present" and "which" insert --invention--.

At page 31, line 6, at the beginning of line 6 change "ommunicates" to --communicates--.

At page 33, line 28, between the words "supply" and "is" insert --76--.

At page 40, line 13, between the words "and" and "are" change "740" to --748--.

At page 44, line 32, between the words "extend" and "far"

change "a" to --as--.

IN THE CLAIMS

1. (Twice Amended) A biological reaction apparatus for dispensing a selected reagent directly to a sample, said biological reaction apparatus [having] comprising:

a reagent carousel having a plurality of reagent container supports thereon;

homing and indexing means, operatively coupled to the reagent carousel, for identifying the position of each reagent container support with reference to a home position; and

drive means, engaging the reagent carousel and operatively coupled to said homing and indexing means, for rotating the reagent carousel and positioning a preselected reagent container support in a reagent supply zone wherein said reagent supply zone is oriented so that a reagent in a container in said preselected reagent container support is dispensable directly to a sample.

2. (Twice Amended) The biological reaction apparatus of Claim 1 wherein the reagent carousel is rotatably mounted on a reagent carousel support and the homing and indexing means further comprises a proximity sensor [detection means] and an object detectable by the proximity sensor [detection means] when the proximity sensor [detection means] and said object are in close proximity, one of said object and said proximity sensor [detection means] being mounted on the reagent carousel, and the other of the object and said proximity sensor [detection means] being mounted on the reagent carousel support in a position adjacent the path of the other.

C1

3. (Twice Amended) The biological reaction apparatus of Claim 2 wherein said object is metallic and mounted on the reagent carousel and the proximity sensor [detector] is a metal proximity sensor [detector] mounted on the reagent carousel support.

C2

5. (Twice Amended) The biological reaction apparatus of Claim 1 including a reagent delivery actuator [means] positioned for engaging a reagent container positioned in the reagent delivery zone and initiating delivery of a predetermined volume of reagent from the reagent container directly to said sample.

C3

56. (Amended) An automated biological reaction apparatus comprising:

a rotatable slide support carousel;

a plurality of slide supports mounted on the slide support carousel in a circular array;

drive means engaging the carousel for rotating the carousel;

a reagent delivery [means] combination for applying a predetermined quantity of reagent to a slide positioned, by rotation of the carousel, in a reagent delivery zone;

an evaporation inhibiting liquid application [means] station positioned at the reagent delivery zone, the evaporation inhibiting liquid application [means] station comprising at least one nozzle positioned for directing a stream of evaporation inhibiting liquid onto a preselected evaporation inhibiting liquid impact zone of a slide positioned at the reagent delivery zone;

a vortex [agitation means] mixing assembly positioned at a vortex agitation zone adjacent to the reagent delivery zone and having a nozzle [means] for directing

fluid at the vortex agitation zone of a slide positioned at the vortex agitation zone;

a heat[ing]ed [means] air supply chamber positioned for heating and passing a heated fluid over the slide supports; and

[a] one or more rinse [solution application means] stations positioned at a rinse zone adjacent to the reagent delivery zone, [the] said one or more rinse [solution application means] stations comprising at least one nozzle positioned for directing a stream of rinse liquid onto a rinse solution impact zone of a slide positioned at the rinse zone; and

a draining means for draining rinse solution from a slide.

C3

60. (Amended) An automated biological reaction apparatus of Claim 59 wherein the vortex [agitation means] mixing assembly is [are] positioned adjacent the inner circumference of the slide support carousel.

C4 SUB I10

63. (Amended) An automated biological reaction apparatus of Claim 56 wherein the drain means comprises a jet drain for [direction] directing a jet of fluid across an upper surface of a slide.

C5

64. (Amended) An automated biological reaction apparatus of Claim 56 wherein [the] said one or more rinse [solution application means] stations comprises a first rinsing means at a beginning of the rinse zone and a second rinsing means at an end of the rinse zone.

SUB I10

65. (Amended) An automated biological reaction apparatus of Claim 64 wherein the first rinsing means includes at least

one nozzle [means] for depositing a layer of rinse liquid onto an upper surface of a slide positioned at the beginning of the rinse zone and the second rinsing means includes sweeping means for sweeping the layer of rinse liquid off of the slide when the slide reaches the end of the rinse zone.

C5 SUB I07

66. (Amended) An automated biological reaction apparatus of Claim 65 wherein the first rinsing means and the second rinsing means are spaced from [on] one another so that a predetermined period of time transpires during the transport of the slide between the first and second rinsing means before the layer of rinse liquid is swept off of the slide.

REMARKS

This Amendment is filed in response to the Office Action dated November 29, 1993. A two-month extension, to expire April 29, 1994, is entered in an attached petition.

Claims 1-81 and 92-93 are pending in the above cited application.

Original Claims 8-55, 68-81 and 92-93 were withdrawn from consideration in response to a restriction requirement.

Claims 82-91 have been canceled.

Claims 4, 6, 7, 57-59, 61-62, and 67 are unchanged.

The specification and Claims 1-3, 5, 56, 60, and 63-66, have been amended as shown above. Additions to the claims are underlined and deletions from the claims are enclosed in square brackets. In the following discussion, all claim line numbers refer to the amended claims as shown above.

Support for the amendments is as follows. Minor changes have been made to the specification to correct typographical errors. No new matter has been introduced as a result of the above changes to the specification.

Claim 1 has been amended in response to the Examiner's

comments. The word "having", in line 3, has been replaced with the word --comprising--.

Claim 2 has been amended in response to the Examiner's comments to recite a --proximity sensor-- rather than "a proximity detection means" in lines 4, 5, 6, 8, and 9. The term --proximity sensor-- is supported in the specification, for example, at page 30, lines 19 and 20.

Claim 3 has been amended for consistency of claim terminology. In lines 3 and 4 the term "proximity detector" has been replaced with the term --proximity sensor--. The new term is supported in the specification, for example, at page 30, lines 19 and 20.

Claim 5 has been amended for clarification. In line 2, the term "reagent delivery actuator means" has been replaced with the term --reagent delivery actuator--. The new term is supported in the specification at, for example, page 23, lines 21-23 and in Figure 15.

Claim 56 has been amended in response to the Examiner's comments. At lines 11 and 13, the term "evaporation inhibiting liquid application means" has been replaced with the term --evaporation inhibiting liquid application station--. Support for the new terminology is found in the specification at, for example, page 21, line 22 and page 22, line 26.

Claim 56 has been further amended in response to the Examiner's comments. At line 18, the term "vortex agitation means" has been replaced with the term --vortex mixing assembly--. Likewise, Claim 60 has been amended in an identical manner, at line 2, to promote uniform terminology in the claims. Support for the new terminology is found in the specification at, for example, page 25, line 29.

Claim 56 has been further amended in response to the Examiner's comments. At lines 26 and 28, the term "rinse solution application means" has been replaced with the term

--one or more rinse stations--. Likewise, Claim 64 has been amended in an identical manner, at line 2, to promote uniform terminology in the claims. Support for the new terminology is found in the specification at, for example, page 19, line 32, page 20, line 26, page 21, line 21 and in Figure 13.

Claim 56 has been further amended for the purpose of clarification. At line 8, the term "reagent delivery means" has been replaced with the term --reagent delivery combination--. The new term is supported in the specification at, for example, page 23, line 21.

Claim 56 has been further amended for the purpose of clarification. At line 20, the term "nozzle means" has been replaced with the term --nozzle--. Likewise, Claim 65 has been amended in a similar manner, at line 2, to promote uniformity in the claim terminology. The new terminology is supported in the specification at, for example, page 26, lines 2 and 3.

Claim 56 has been further amended for the purpose of clarification. At line 23, the term "heating means" has been replaced with the term --heated air supply chamber--. The new term is supported in the specification at, for example, page 24, line 29.

Claim 63 has been amended to correct a typographical error. At line 3, the word "direction" has been replaced with the word --directing--.

Claim 66 has been amended to correct a typographical error. At line 3, the word "on" has been replaced with the word --one--.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-7 and 56-67 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to Claim 1 the Examiner states:

> In claim 1, line 3, it is not clear whether the claim is meant to be open-ended since 'having' has been used as the transition term. The examiner recommends --comprising-- or --consisting of-- for clarification.

As requested by the Examiner, Claim 1 has been amended and the word "having" ,in line 3, has been replaced with the word --comprising--.

With respect to Claim 2, the Examiner states:

> In claim 2, line 5, the use of 'means' is improper because it does not include the 'means for' plus function format. In line 7, 'close proximity' is an indefinite location.

Claim 2 has been amended in response to the Examiner's comments to recite a --proximity sensor-- at lines 4, 5, 6, 8, and 9 rather than "a proximity detection means." Claim 3 has likewise been amended and the term --proximity sensor-- has replaced the term "proximity detector" in lines 3 and 4 to promote uniformity of terminology within the claims. As amended, Claim 2 does not contain the term "means" and therefore Claim 2 is believed to be clear and definite.

The rejection of Claim 2 on the grounds that "close proximity", as used in line 7, is "an indefinite location" is respectfully traversed. The phrase "close proximity" is believed to be clear and definite when read in light of the specification which, at page 30, lines 18-23, states:

> Indexing block 229 is a metal block. Proximity sensor 610 is supported on the underside of plate 22 by bracket 611. The proximity sensor 610 emits an electrical signal through leads 612 which changes when the metal block 229 is positioned in the 'home' position immediately above the sensor.

As described in the above quoted portion of the specification, the "close proximity" is the distance at which "an object detectable by the proximity sensor" (in this case

the metal block 229) is close enough to the proximity sensor to interact with the electrical signal produced by the proximity sensor and emitted trough the proximity sensor leads. This distance is determined by the amplitude of the electrical signal produced by the proximity sensor and the position of the proximity sensor leads which emit the signal. Both the amplitude of the signal and the placement of the leads is variable from embodiment to embodiment and can be changed within a specific embodiment. However, for a given configuration of a particular embodiment, the term "close proximity" is clearly defined as described above. Therefore, withdrawal of the rejection of Claim 2 based on the use of the term "close proximity" is respectfully requested.

With respect to Claim 56 the Examiner stated:

> In Claim 56, lines 12, 20, and 27, the use of 'means' is improper because it does not include the 'means for' plus function format.

In response to the Examiner's comments, Claim 56, at lines 11 and 13, has been amended and the term "evaporation inhibiting liquid application means" has been replaced with the term --evaporation inhibiting liquid application station--. As amended, Claim 56 does not contain the term "evaporation inhibiting liquid application means" and therefore Claim 56 is believed to be clear and definite.

In response to the Examiner's comments, Claim 56, at line 18, has been further amended and the term "vortex agitation means" has been replaced with the term --vortex mixing assembly--. Likewise, Claim 60 has been amended in an identical manner, at line 2, to promote uniform terminology in the claims. As amended, Claims 56 and 60 do not contain the term "vortex agitation means" and therefore Claims 56 and 60 are believed to be clear and definite.

In response to the Examiner's comments, Claim 56 has been

further amended at lines 26 and 28. The term "rinse solution application means" has been replaced with the term --one or more rinse stations--. Likewise, Claim 64 has been amended in an identical manner, at line 2, to promote uniform terminology in the claims. As amended, Claims 56 and 64 do not contain the term " rinse solution application means" and therefore Claims 56 and 64 are believed to be clear and definite.

In light of the above amendments to Claims 1-7, the Applicants respectfully submit that the claims currently pending in the application comply with the requirements of 35 U.S.C. § 112, second paragraph, and withdrawal of the rejection of Claims 1-7 is respectfully requested.

Furthermore, with respect to Claims 56-67 the Examiner has stated: "Claims 56-67 would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C., § 112." Therefore, in light of the above amendments to Claims 56-67, allowance of Claims 56-67 is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 1-3 and 5-6 were rejected under 35 U.S.C. § 103 as being unpatentable over Wakatake et al in view of Assmann et al. The Examiner has stated:

> Wakatake et al discloses the instant invention substantially as claimed. Wakatake et al teaches an automatic analyzer having a reagent carousel (30) having a plurality of reagent containers (32), a homing and indexing means and stepper motor (see column 4, lines 8-17), and drive means engaging the reagent carousel (34). Wakatake et al fails to teach the reagent is dispensed directly to a sample.
>
> Assmann et al teaches an automatic analyzer having a primary vessel on a moveable carriage. The primary vessel (9) contains a reagent (see abstract) and is directly passed to a sample in order to avoid contamination.

> It would have been obvious to one having ordinary skill in the art to replace the reagent containers of Wakatake et al with the primary vessels as taught by Assmann et al thereby eliminating the transfer device in order to avoid cross contamination.

The rejection of Claims 1-3, and 5-6 over Wakatake et al in view of Assmann et al is respectfully traversed. Neither Wakatake nor Assmann teach or suggest the combination of the two references. Indeed, as described below, the two systems involve incompatible referencing and indexing systems, with Wakatake teaching variable reagent container and sample positions, while Assmann depends on stationary reagent container and sample positions. Further, as also described below, even if Wakatake and Assmann were combined, as the Examiner suggests, the resulting system would not include "a reagent supply zone" or have the present invention's novel capability to dispense reagent "directly to a sample."

In Claim 1, Wakatake teaches "a sample table," "a reaction table," and "at least a pair" of reagent tables. The sample table, reaction table, and reagent tables are each "operatively connected" to a respective drive means which "rotates" the respective table "in a stepping manner" to bring the reagent or sample containers on the respective tables "sequentially" to "predetermined" positions. (Wakatake at Claim 1, lines 25-60.) The rotation and position of the various containers on the respective tables is synchronized and controlled by a computer which monitors the sequential position of each sample and reagent container so that the proper reagent from the proper reagent container is delivered into the proper sample. This operation is described in detail in Wakatake at Column 7, lines 18-24 which reads as follows:

> The timed operation of the sample pipetting device 40 and reagent pipetting device 50, along with the rotation of the sample table 10, reaction table 20 and reagent tables

> 30, may preferably be controlled by a properly designed microcomputer program in conjunction with suitable sensing means for identifying each sample or chemical container on the tables.

Thus, as set forth in Claim 1, and described in the specification, Wakatake is a system which is designed around reagent and sample containers whose positions are varied at regular intervals by the sequential rotation of the tables holding the containers.

In contrast, Assmann teaches a "carrier means" which engages one of a "plurality of primary vessels," orients the primary vessel for dispensing reagent and then transfers the primary vessel to the **fixed position** of one of a "plurality of secondary vessels." A portion of the contents of the primary vessel is then dispensed. Once the reagent is dispensed, the carrier means returns the primary vessel to its original location, re-orients the primary vessel to its storage position and then **returns the primary vessel to its starting position.** (Assmann in Claim 1, in the Abstract, lines 12 and 13, at Column 5 lines 53-57, and in Figures 1 and 2). In short, Assmann teaches a device which relies on the primary vessels having fixed storage positions and the secondary vessels remaining stationary, with fixed coordinates in the "x-y plane." (Assmann at Column 5, lines 39-44).

Thus, the Wakatake system of rotating and dynamic container coordinates is incompatible with Assmann which requires fixed and static container coordinates. Applicants therefore respectfully submit that there is no suggestion, in either reference, to those of ordinary skill in the art to combine these two references. Further, Applicants do not believe Wakatake and Assmann could be combined in a working and practical system because the two references appear to teach away from such a combination by describing incompatible referencing and indexing systems as set forth above.

However, even in the unlikely event that Wakatake and Assmann were successfully combined into one system, the resulting system would still lack the present invention's novel capability to dispense reagent **"directly to a sample"** as set forth in Applicants' Claim 1, at line 16.

The present invention recites "a reagent carousel having a plurality of reagent container supports thereon" and a "drive means" wherein said drive means engages the carousel:

> for rotating the reagent carousal and positioning a preselected reagent container support in a **reagent supply zone** wherein said reagent supply zone is oriented so that **a reagent** in a container in said preselected reagent container support **is dispensable directly to a sample.**
>
> (Claim 1, lines 10-16, emphasis added)

As shown above, the recited apparatus provides for **direct** dispensing of reagent from a reagent container to a sample. An exemplary reagent carousel and reagent supply zone which are encompassed by Applicants' Claim 1 are shown in Figures 1, 2, 3, 15 and 16 of the application. The present invention uses the "drive means" to rotate the "reagent carousel." The reagent carousel holds the reagent containers. As can be seen in the Figures, the Reagent carousel is positioned above the samples and the reagent containers are oriented within the carousel with their outlet nozzles pointing down such that they are ready to dispense reagent directly to the sample below. The reagent container remains positioned within the carousel before, during, and after the dispensing of reagent and the reagent containers are generally removed from the reagent carousel only to be refilled or replaced. Thus, once the reagent carousel is rotated into position by the drive means, with the desired reagent container positioned above the reagent supply zone, no further mechanical manipulation to position or orient the reagent container is required. Further, once one reagent is dispensed, the carousel can be immediately rotated

to dispense a second, third, or Nth reagent without ever removing a reagent container from its position in the carousel.

In contrast, Wakatake et al teaches reagent tables positioned side by side with a reaction table. (Wakatake et al, Figure 2). **This side by side configuration precludes dispensing of the reagent "directly to the sample" or the incorporation of a "reagent delivery zone"** as set forth in Claim 1 of the present invention. The Wakatake side by side configuration requires an additional device, a reagent pipetting device, to transfer the reagent between tables and mediate the dispensing of reagent to the sample. The reagent pipetting device is used to suck up an aliquot of reagent from a reagent container on one of at least two reagent tables, pivot so that the pipetting tube of the device is held just above a selected reaction vessel on a separate reaction table, and dispense the aliquot of reagent to the vessel (Wakatake at column 4, line 42 to column 5, line 10). Such devices are referred to in the trade as "sip and spit" devices. A rinse step is required to clear residual reagent from the pipetter tubing following dispensing of the reagent (Wakatake at column 4, lines 57-65). The dispensing of reagents from the reagent tables to the reaction table of Wakatake requires more steps and therefore, more time, than does the direct dispensing system of Applicants' Claim 1. Additionally, the rinse step in Wakatake may leave traces of reagent in the pipetter tubing which can result in cross-contamination of reagents.

As described above, Wakatake teaches reagent tables and a reaction table that are situated side by side, a configuration which makes direct dispensing of reagent impossible. Any system involving the Wakatake side by side tables will require either a pipetter as set forth in Wakatake, or involve a system to transport the reagent containers themselves from the reagent tables to the reaction table and then back to the reagent

tables once the reagent has been dispensed. Therefore, any system based on Wakatake will inherently lack the present invention's novel capability to dispense reagent "directly to a sample."

The combination of Assmann and Wakatake would merely aggravate the situation because Assmann teaches a system where, in order to dispense reagent, the reagent container must be rotated 180° so that the "pourer nozzle" is pointed downwards (Assmann in Claim 1 at lines 16-20 and, at column 5, lines 46-56, and in Figure 2). After rotating the reagent container, Assmann uses a transporting carriage, holding the reagent container, to the sample or "secondary vessel" (Assmann in the abstract and, at column 5, lines 39-44, and Figures 1 and 2). This action is described in Claim 1 of Assmann, at lines 16-20, as follows:

> said carrier means further having means for rotating said primary vessel 108 [180] degrees about an axis that is perpendicular to the longitudinal axis of said primary vessel so that said open end points downwardly;

Thus, as described in Claim 1 itself, with the apparatus and method of Assmann, the reagent containers or "primary vessels" are stored in an upright position, 180° opposite to their dispensing positions. This means that in order to use an Assmann device with the apparatus of Wakatake, each reagent container would have to be located on the reagent table and engaged individually by Assmann's "clamping means" , then rotated 180° into the dispensing position, then moved from the reagent table to the dispensing location on the reaction table, then activated to dispense reagent, and then rotated 180° back to the upright position and placed back in the reagent table. This process would have to be repeated for each reagent applied. Applicants respectfully submit that this process would not represent dispensing of reagent

"directly to a sample" as set forth in Applicants' Claim 1. Therefore, combining Assmann with Wakatake does not cure Wakatake's shortcomings.

As set forth above, the combination of Wakatake and Assmann, if such a combination could even be made, still fails to teach or suggest a "reagent supply zone" or the capability to dispense reagent "directly to a sample." Additionally, with the system envisioned by the Examiner, the time involved for application of each reagent would be considerably longer than with the present invention. This is more problematic than a simple inefficient use of time because many processes require heating the sample environment during reagent application. Wakatake itself allows for sample and reagent heating. This heating brings with it the risk of sample dehydration and destruction as described in the Applicants' application at, for example, page 2, lines 5-9. The extra time spent waiting for the Assmann device to locate, rotate, position, dispense, re-rotate, and replace the reagent container would result in each sample being exposed for longer periods to the artificially elevated temperatures. In cases involving the application of several reagents to the same sample, such as in situ DNA analysis, this extra time could result in sample destruction or, at the very least, require the addition of elaborate and inefficient anti-dehydration measures. The apparatus of the present invention minimizes the problem by employing a reagent carousel and reagent container supports, as described above, which minimize the time required to apply a given reagent, and the time between the application of multiple reagents, by dispensing reagent "directly to a sample."

Thus, having the capability of dispensing reagent "directly to a sample" through a reagent carousel avoids the need for a transfer/dispensing device and saves precious time, which in turn allows for sample treatment and analysis which

might be impossible using a system created by the combination of Wakatake and Assmann as suggested by the Examiner.

As shown above, neither Wakatake or Assmann suggest to those of skill in the art that the references could or should be combined. Further, as shown above, even in combination, Wakatake and Assmann neither teach nor suggest a "reagent supply zone" nor the capability of dispensing reagent "directly to a sample." Therefore, Claims 1-3, and 5-6 are patentably distinct over Wakatake et al in view of Assmann et al and withdrawal of the rejection of Claims 1-3 and 5-6 is respectfully requested.

Claim 4 was rejected under 35 U.S.C. § 103 as being unpatentable over Wakatake et al '055 in view of Assmann et al as applied to Claims 1-3 and 5-6 above, and further in view of Jordan. In view of the discussion above with respect to Wakatake et al and Assmann et al, Applicants respectfully traverse the rejection of Claim 4, over Wakatake et al in view of Assmann et al and further in view of Jordan. Further, Applicants respectfully submit that Jordan uses the bar code and bar code reader in a manner significantly different than that described by Applicants, which manner does not cure the deficiencies in the Wakatake and Assmann references.

Claim 4 recites the "biological reaction apparatus of Claim 1" which also incudes a "bar code zone" and "homing and indexing means" further comprising:

> a bar code reader mounted on the reagent carousel support in a position to read a bar code **on a reagent container** positioned in the bar code zone...
>
> (Claim 4, lines 5-8, emphasis added)

Since Claim 4 is dependent on Claim 1, Claim 4 recites a "biological reaction apparatus" which includes a "reagent supply zone" and the capability of dispensing reagent "directly to a sample." As described above, the combination of Wakatake

and Assmann neither teaches nor suggests a "reagent supply zone" nor the capability of dispensing reagent "directly to a sample." The addition of the Jordan reference to this combination does nothing to cure this basic deficiency.

Jordan teaches a "multiple dose reagent pack and corresponding carousel" for use with existing automatic analyzers. (Jordan in the Abstract). The Jordan device is designed for use with systems incorporating "pipetting means" such as that described in Wakatake. (Jordan at Column 1, lines 45-48). Jordan even addresses the problem of cross contamination, described above, inherent in systems utilizing "pipetting means" and, in one embodiment, the Jordan device includes a position in the "reagent pack" for a "wash or buffer reagent that can be used to rinse the pipetting means after it accesses each reagent." (Jordan at Column 5, lines 35-45). Nothing in the Jordan reference teaches or suggests the present invention and the capability of dispensing reagent "directly to a sample." Therefore, Claim 4 is patentably distinct over Wakatake et al in view of Assmann et al and Jordan based on this difference alone.

However, Jordan teaches the use of a "labeling means" including an "optical bar code" which is attached to the outer surface of the "retaining wall" of the "vial carrier" and not to the vials themselves. This is in contrast to the wording of Applicants Claim 4 which, as shown above, provides for "a bar code on a reagent container..." Thus, Jordan uses the bar code to identify the "vial carrier," which can include several reagent containers, while the present invention uses the bar code to identify and locate the individual reagent containers. Applicants therefore respectfully submit that their use of the bar code and bar code reader is patently distinct over the use described in Jordan and the combination of Jordan, Wakatake, and Assmann and withdrawal of the rejection of Claim 4 is again

respectfully requested.

Claim 7 was rejected under 35 U.S.C. § 103 as being unpatentable over Wakatake et al '055 in view of Assmann et al as applied to Claims 1-3 and 5-6 above, and further in view of Barker et al or Hollar et al. The Examiner has stated:

> The combination of Wakatake et al in view of Assmann et al discloses the instant invention substantially as claimed, but fails to [teach] that the support tray has indexing support feet.
>
> Hollar et al and Barker et al each teach the use of indexing feet to support tray on a carousel.
>
> It would have been obvious to one having ordinary skill in the art to add indexing feet as taught by Hollar et al or Barker et al to the device of Wakatake et al and Assmann et al in order to provide a removable tray that can be removed from the carousel and stored between uses.

In view of the discussion above with respect to Wakatake et al and Assmann et al, the Applicants respectfully traverse the rejection of Claim 7, over Wakatake et al in view of Assmann et al and further in view of Hollar et al or Barker et al.

Claim 7 recites a reaction apparatus with a "reagent carousel" including a "reagent tray support" and a "reagent support tray" which has "**indexing** support feet." The interaction of the reagent support tray indexing support feet, reagent tray support "receptors", and reagent carousel, as well as the dual functions of support and indexing performed by the "indexing support feet", is set forth in the language of Claim 7 which reads as follows:

> The biological reaction apparatus of Claim 1 wherein the reagent carousel comprises a reagent support tray removable supported by a reagent tray support, the reagent support tray has indexing support feet on an underside thereof, the reagent tray support has receptors for the indexing support feet in an upper surface thereof, **whereby the reagent support tray can be removed from the reagent tray support for reloading or refrigerated storage and can be replaced on**

the reagent support tray in the same indexed position.

(Emphasis added)

An exemplary "reagent support tray" which is encompassed by Applicants' Claim 7 is shown in Figure 20A of the application. As described in the language of Claim 7 above, the reagent support tray indexing support feet serve two purposes. First, the "indexing support feet" provide support for the "reagent support tray" when the "reagent support tray" is removed from the "reagent carousel" and "reagent tray support." This function allows for stable storage of the "reagent support tray' in a refrigerator or other storage area. Second, the "indexing support feet" fit into matching "receptors" in the "reagent tray support." The "receptors" and "indexing support feet" are designed such that the "reagent support tray" can be placed into the "reagent tray support", and thereby coupled to the "reagent carousel", in only one position. This feature insures that the "reagent support tray" and reagent containers are always replaced in a **"same indexed position"** with a predetermined orientation on the "reagent tray support" of the "reagent carousel." This allows the apparatus of the invention to position the correct reagent container, and dispense the proper reagent, even after the "reagent support tray" has been removed from the "reagent carousel", stored or refilled, and then replaced on the "reagent carousel.'

In contrast, Hollar et al teaches the use of a "reaction cuvette holder" which has a "depending slotted portion." The Hollar system serves to secure a "containment means" to the carousel. The "containment means" consists of "pie slice" shaped cylinder portions, a plurality of which can be coupled to the carousel, which include sample/reagent holding regions (Hollar column 5, line 66 to column 6 line 38 and Figures 6 and

7). In Hollar, the system of "reaction cuvette holder" and "depending slotted portion" is simply a means of securing the "containment means" to the carousel. No mechanism or method for ensuring the "containment means" is returned to the "same indexed position" is suggested. Therefore, Applicants respectfully submit that Hollar et al neither teaches nor suggests the use of "indexing support feet" as set forth in Claim 7 of the application.

The Examiner has also submitted Barker et al as an example of prior art incorporating the "indexing support feet" of the present invention. However, as with Hollar, Barker fails to disclose "feet" which perform an "indexing" function. Indeed, the system in Barker fails to provide "feet" on the removable "sample sectors" at all. Barker teaches a system of eight support arms. Each support arm includes four cylindrical "upward projections" which secure "pie slice" shaped "sample sectors" onto a "support ring" (Barker column 5, line 54 to column 6, line 2 and Figures 1 and 2). Barker provides no mechanism for "indexing" the position of the "sample sectors" and thereby ensuring the "sample sectors" are placed in the "same indexed position" when they are replaced on the "support ring." Further, the "upward projections" in Barker extend from the "support ring", thus, the "sample sectors" themselves have no "upward projections" or "feet." Thus, the "upward projections" of Barker do not even provide support for storage of the "sample sectors" once they are removed from the "support ring." Therefore, the Applicants respectfully submit that Barker et al neither teaches nor suggests the use of "indexing support feet" as set forth in Claim 7 of the application.

As set forth above, the reagent carousel of Claims 1-7 is neither taught or suggested by Wakatake et al in view of Assmann et al or further in view of Barker et al or Hollar et

al. Withdrawal of the rejection under 35 U.S.C. § 103 and allowance of Claims 1-7 is therefore respectfully requested.

All of the rejections in the Office Action having been overcome, it is believed that the application is now in condition for allowance. Early notice to that effect is respectfully requested. If a telephone conference would expedite the prosecution of this application, the Examiner is requested to telephone and confer with the undersigned attorney.

Respectfully submitted,

Laura Terlizzi

Laura Terlizzi
Attorney for Applicants
Reg. No. 31,307

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on April 29, 1994.

Laura Terlizzi
Attorney for Applicants

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 97,008-U)

In re Application of:		
COPELAND, et. al		Group Art Unit: 1743
Serial No.:	09/452,309	Examiner: Bex, P.
Filed:	August 5, 1997	
For:	Automated Biological Reaction Apparatus	

Commissioner for Patents
Washington, DC 20231

AMENDMENT

Dear Sir:

Applicants hereby respond to the Office Action dated May 10, 2001.

IN THE CLAIMS:

Please amend claims 81, 88, 94, 99, 105 and 107 as follows. A marked up version of the amended claims, to show all the changes, is attached hereto on pages separate from the amendment in accordance with 37 CFR 1.121(c)(1)(ii).

81. (Amended) The method of claim 80 wherein the slide bar code identifies a slide sample placed on the slide and identifies a sequence of reagents for the slide sample.

88. (Amended) A method of dispensing reagents onto a slide, the method comprising the steps of:

providing a plurality of reagent containers in a reagent support, each of the reagent containers having a reagent barcode;

providing slides on a slide support, the slides having at least one slide bar code;

providing a bar code reader;

reading the bar codes on the reagent containers;

determining reagents in the reagent containers based upon the reading of the bar codes on the reagent containers;

reading the slide bar codes on the slides;

determining a sequence of reagents to be applied on the slides based upon the reading of the slide bar codes on the slides; and

dispensing the reagents in the reagent containers based upon the sequence of reagents to be applied.

94. (Amended) A method of dispensing reagents onto a slide, the method comprising the steps of:

providing at least one reagent container;

providing at least one slide on a slide support;

automatically identifying the reagent container using a computer;

automatically determining whether the reagent in the reagent container should be dispensed onto the slide;

moving the reagent container and the slide support relative to one another to position the reagent container over the slide; and

dispensing the reagent in the reagent container onto the slide based on the determination of whether the reagent in the reagent container should be dispensed onto the slide.

99. (Amended) An automated biological staining apparatus comprising:

a slide support for holding slides;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

bar code reader;

reagent dispensing device for applying reagent onto a particular slide; and

computer in communication with the slide support drive means, the reagent drive means, bar code reader and means for dispensing reagent,

wherein the bar code reader reads reagent bar codes on the reagent containers and slide bar codes on the slides, and

wherein the computer automatically determines whether reagent in the reagent containers should be dispensed onto the particular slide.

103. (Amended) The automated biological staining apparatus of claim 99 wherein the bar code reader reads slide bar codes on the slides and wherein the slide bar codes are sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the particular slide.

104. (Amended) The automated biological staining apparatus of claim 99 further comprising:

homing device connected to the slide support and in communication with the computer wherein the homing device determines position information for the particular slide.

105. (Amended) The automated biological staining apparatus of claim 99 wherein the computer controls the movement of the reagent tray and the slide support to move relative to one another to position the reagent containers over the particular slide.

107. (Amended) An automated biological staining apparatus comprising:

a slide support for holding slides;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

means for automatically identifying the reagent containers;

means for automatically determining whether reagent in the reagent containers should be dispensed onto a particular slide; and

reagent dispensing device for applying reagent onto a particular slide.

109. (Amended) The automated biological staining apparatus of claim 107 wherein means for automatically determining whether reagent in the reagent containers should be dispensed onto the slide includes a bar code reader, wherein the bar code reader reads slide bar codes on the slides and wherein the

slide bar codes are sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the particular slide

REMARKS

Applicants wish to thank Examiner Bex and Supervisory Patent Examiner Warden for the personal interview conducted on June 21, 2001. Claims 72-113 are in the application for consideration.

Claim Rejections – 35 U.S.C. §112

In Paragraph 4 of the Office Action, claims 81, 89-93 and 99-113 were rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention." Specifically, the terms "histochemical process" (claim 81), "reading the bar code on the slide" (claim 88), "a slide support for holding slides" (claims 99 and 107), "the slides" (claims 103-105 and 109), "the computer moves" (claim 105), "means for automatically determining whether reagent in the reagent containers" (claim 107), and "computer in communication with . . . the means for automatically determining whether reagent in the reagent containers should be dispensed." Applicants have amended claims 81, 88, 99, 103-105, 107 and 109 where it is believed appropriate.

Claim Rejections – 35 U.S.C. §102

In Paragraph 6 of the Office Action, claims 72, 84-87, 94, 97-98, 107, 110 and 112 were rejected under 35 U.S.C. §102(b) as being anticipated by Bogen et al. (U.S. Patent No. 5,645,114).

The Examiner asserted that the Bogen patent discloses an automated method and apparatus for immunocytochemistry comprising a rotatable slide support carousel 504 for mounting a plurality of slide

supports 532 comprising samples, a drive means for rotating the slide support carousel, a reagent rotor 504 positioned above the slide rotor and a plurality of reagent containers. The Examiner further asserts that the reagent containers for applying a predetermined quantity of reagent onto the slide is based on programming containing histochemical protocols regarding the particular reagent to be used on the sample. As support, the Examiner states that Bogen discloses the use of a program which supplies the microprocessor with information regarding the location of the reagents on the reagent rotor and the location of slides on the slide rotor.

As an initial matter, the Bogen '114 patent is not prior art to the present application. The Bogen '114 patent was filed on May 31, 1994 as Application Serial No. 08/251,597 and is a continuation-in-part of Application Serial No. 07/881,397 filed on May 11, 1992 (now U.S. Patent No. 5,316,452). By contrast, the present invention claims priority to Application Serial No. 07/488,601 filed on March 2, 1990. A copy of Application Serial No. 07/488,601 is enclosed. Therefore, the Bogen '114 patent is not prior art to the present invention.

Some examples, though not exhaustive, of the support found in Application Serial No. 07/488,601 are as follows:

> The apparatus preferably has bar code readers positioned to read bar codes on the sample containers or slides and on the reagent containers. (page 5, lines 17-19).
>
> The automated immunostaining apparatus of this invention performs all steps of immunohistochemical and *in situ* DNA assays irrespective of complexity or their order, at the time and temperature, and in the environment needed. Specially prepared slides containing a bar code identifier and a mounted tissue section are placed in special support on a carousel, subjected to a preprogrammed sequence of reactions, and are removed from the carousel, ready for examination. (page 10, lines 8-17).
>
> Bar code reader 231 above slide 205 reads a slide bar code 233 (Figs. 13 and 17) on each slide. The slide bar codes identifies the slide sample and the particular immunohistochemical process required for that sample. This information is fed into the computer and correlated with the indexed position of that slide with respect to "home", to control the sequence of reagent chemicals to be applied to that slide in the reagent application zone. (page 17, lines 13-20).

> Bar code reader 346 can be mounted on post 302, positioned to scan a bar code 348 on the reagent container 12. Bar code 348 identifies the contents of the reagent bottle. At the beginning of a slide treatment operation, the reagent carousel 10 is rotated by the bar code reader 346, and the bar code on each reagent bottle is scanned. The scanned information is fed to the computer and correlated with the indexed position of the reagent carousel 10. This information is used to rotate the reagent carousel 10 to place the correct reagent bottle in the application zone for each slide treatment step for each slide. (page 23, lines 3-14).
>
> The computer RS-232 I/O port 770 sends polling signal to the slide barcode reader 231 and receives signals indicating bar code information read through line 772. Similarly, the computer RS-232 I/O port 770 sends polling signal to the reagent carousel barcode reader 346 and receives signals indicating barcode information read through line 774. (page 37, lines 7-13).
>
> Preparing the slides, including applying a bar code to the slide indicating the immunohistochemical process to be used with the sample, and manually rinsing and applying evaporation inhibiting liquid to the tissue sample surface before placement in the apparatus to prevent dehydration of the sample. (page 37, lines 27-32).

See also Figures 13, 14, 15, 16 and 17.

Moreover, Applicants do not believe that the Bogen patent anticipates any of the claims of the present invention. Bogen discloses only that "[a] microprocessor, not shown, controls the entire dispensing assembly 500." A minimal discussion of the microprocessor is disclosed wherein it is provided that "an operator programs the microprocessor with the information such as the location of the reagents on the reagent rotor and the location of slides on the slide rotor. The operator then programs the particular histochemical protocol to be performed on the tissue samples." (col. 8, lines 1-15). No further explanation of the microprocessor, e.g. its type, how it is interconnected, or how it specifically operates, is provided.

Bogen does not teach or even suggest **automatically** identifying the reagent container using a computer or **automatically** determining whether reagent in the reagent container should be dispensed onto the slide. Instead, Bogen teaches a system which relies, at least in part, on data entry from the operator. Specifically, in Bogen the operator "programs the microprocessor with the information such as the locations of reagents" (col. 8, lines 2-4) or "programs the particular histochemical protocol to be performed on the tissue samples." (col. 8, lines 5-6). For example, the operator programs that for

reagent container position 1, reagent "A" is selected. Likewise, for slide position 1, histochemical protocol "z" is selected. The operator must then load reagent container position 1 with reagent "A" and slide position 1 with a slide requiring histochemical protocol "z". Otherwise, the system will work incorrectly. In fact, the Bogen system does not teach **any** steps of **automatic** identification or **automatic** determination. Rather, the computer runs its program under the assumption that the operator placed the reagent containers and the slides in their pre-programmed positions (*i.e.*, the operator has entered "data" in the form of placing the reagent containers and slides in the proper positions) and does not bother to check if, in fact, the reagents or slides are in their proper positions.

By contrast, the present invention automatically identifies the reagent container using a computer and automatically determines whether reagent in the reagent container should be dispensed onto the slide. The present invention does not rely on any form of data entry from the operator (*e.g.*, the placement of the reagent containers or slides in the pre-assigned positions). Thus, the claimed invention is not anticipated by the Bogen reference.

Rejection based on Stark, Sakurada and Saralegui references

In Paragraph 9 of the Office Action, claims 72-83, 86-93, 99-104 and 107-113 were rejected under 35 U.S.C. §103 as being unpatentable over Stark et al. (J. Immunol. Methods 107:89-92 (1988)) in view of Sakurada (U.S. Patent No. 4,346,056) or Saralegui et al. (U.S. Patent No. 5,439,645).

The Examiner asserted that the Stark reference discloses an automated method and apparatus for immunocytochemistry, the apparatus comprising a rotatable slide support carousel, drive means, and reagent containers. The Examiner further stated that the Stark reference fails to specifically recite sensors for detecting positions of slide samples or reagent containers or a bar code reader for identifying types of reagents.

With respect to Sakurada, which the Examiner combined with Stark in asserting that Applicants' claimed invention is obvious, the Examiner asserted that Sakurada discloses the rotation position of the reagents and the different types of reagents used, which are detected and identified by sensors. With respect to Saralegui, the Examiner asserted that Saralegui et al. teaches a plurality of sample containers on a carousel, the sample containers comprising bar code labels for identifying the appropriate process for the sample and teaches the use of electro-mechanical sensors to detect when the carousel is at the home position.

Applicants respectfully disagree with the Examiner and submit that neither the combination of Stark and Sakurada nor the combination of Stark and Saralegui render the Applicants' claimed invention obvious. Neither combination discloses or suggests all of the elements of Applicants' invention as disclosed and claimed.

The Stark reference, as discussed in the background section of the current application, describes a microprocessor controlled system including a revolving table or carousel supporting radially positioned slides. A stepper motor rotates the table, placing each slide under one of the stationary syringes positioned above the slides. The microprocessor is programmed prior to the beginning of the staining procedure, as disclosed in the following excerpts from the Stark reference:

> The software to control the device was written in Assembler and the dialogue with the operator was via a standard terminal. At the start of the program the actual processing sequence could be programmed individually or, alternatively, this part of program could be deleted and a previously stored procedure requested. **For each specimen the number of slides and the names of the primary antisera were entered. The slides were inserted one after the other and the table advanced one position by actuating a pedal switch.** When all of the slides were inserted, the program requested that the pipetting units with the syringes be filled with the appropriate antibody solutions. Then the application of the primary antibody was requested. **In order to avoid errors the name of the antibody was indicated on the screen and all slides designated to receive this antibody were successively moved to the window in the lid of the device.**
>
> * * *

The expenditure of work was considerably reduced and manual work was only necessary at the start and before the end of the staining procedure.

Page 91, columns 1-2 (emphasis added). The Stark reference teaches that the specific positions in the carousel are pre-programmed with the processing sequence. Prior to the beginning of a staining procedure, the Stark reference thus requires the entry of the slides in specific positions to match the pre-programmed sequence assigned for each of the specific positions.

Stark does not teach or even suggest **automatically** identifying the reagent container using a computer. Stark merely teaches **manual** identification of the reagent containers. Specifically, Stark teaches that the pipetting units be manually filled in predetermined syringes with antibody solutions necessary for the staining process. During a staining run, the computer in Stark does not "identify" the reagent container. Rather than automatically identifying, the programming in Stark assumes that the proper reagent was manually inserted. Moreover, Stark does not teach or even suggest **automatically** determining whether reagent in the reagent container should be dispensed onto the slide. Rather, Stark only teaches that the slides must be **manually** inserted in the proper positions based the preprogrammed sequence assigned to a particular slide position. Again, the programming in Stark does not automatically determine whether to apply reagent. Rather, the programming assumes that the proper slide was manually inserted into the proper position.

The Sakurada reference teaches the use of absolute positioning for identifying reagent vessels. The Sakurada reference requires that each time a position must be sensed, a light must be shown through the holes, as shown in Figures 7a-c. Sakurada does not disclose, or even suggest, automatically identifying the reagent container, based at least in part on information from the reagent container, using a computer. Rather, Sakurada identifies the reagent container based on its absolute position, not on any information on the reagent container. Moreover, Sakurada does not disclose, or even suggest, automatically determining, based at least in part on information from the slide, whether reagent in the

reagent container should be dispensed onto the slide. The Saralegui reference has a filing date of January 25, 1993. As discussed above, the current invention claims a filing date of March 2, 1990. Therefore, the Saralegui reference is not prior art to the present invention.

In contrast to Stark et al., Sakurada and Saralegui et al. taken alone or in any combination, Applicants disclose and claim in independent claims 72 and 94 a "method of dispensing reagents onto a slide" comprising "automatically identifying the reagent container using a computer" and "automatically determining whether reagent in the reagent container should be dispensed onto the slide". Moreover, claim 88 recites a "method of dispensing reagents onto a slide" comprising "determining reagents in the reagent containers based at least in part upon the reagent barcodes read on the reagent containers" and "determining a sequence of reagents to be applied on the slides based at least in part upon the slide barcodes read on the slides". These limitations describe an automated system which requires no "data entry" from the operator. The operator, therefore, is not required to place the reagent containers or slides in pre-assigned positions. Instead, the operator need only place the reagent containers on any position in the reagent support. Likewise, the operator need only place the slide in any position on the slide support. This automation is advantageous for at least three reasons: (1) increasing the reliability of the system; (2) reducing the complexity of the operation of the system; and (3) increasing the ability to process more tissue samples without reprogramming.

Reliability of the system

Reliability, without question, is critical in histological staining procedures. Errors often occur when (i) the wrong staining sequence is assigned to a slide; or (ii) the wrong reagent is applied to a slide. Prior art devices, such as the staining device in Stark reference, relied on manually determining whether a particular slide would undergo a particular staining sequence. Specifically, prior to execution of a staining run, staining sequences were programmed for certain slide positions (*e.g.*, position 1 was

programmed with sequence 1, position 2 was programmed with sequence 2, etc.). The operator was thus required to manually place the slide in the predetermined slide position in order to ensure the proper staining protocol (*e.g.*, for staining sequence 2, the operator was required to insert the slide in position 2). Likewise, the prior art, including the Stark reference, relied on manually identifying the reagent container. Specifically, prior to beginning a staining run, the necessary reagents for the staining run were assigned to particular reagent container positions (*e.g.*, position 1 was programmed with reagent 1, position 2 was programmed with reagent 2, etc.). The operator was thus required to insert the proper reagent container in the proper position. By contrast, the automatic identification of the staining protocols and the automatic identification of the reagent containers work in combination to eliminate the need for operator input at the beginning of a staining run. In turn, the present invention significantly reduces the possibility of applying the wrong staining sequence or applying the wrong reagent.

Complexity of the operation of the system

Another important consideration in a staining system is its complexity. Typically, laboratory technicians operate the staining devices and therefore do not wish to operate very complicated machinery. The automatic identification of the staining protocols and the automatic identification of the reagent containers work to significantly reduce the oversight necessary for operation of the system. The laboratory technicians need only insert the slides and the reagent containers into the staining system, and the system is able to process the slides. In contrast, the prior art required careful oversight, requiring the careful placement of the slides and the reagent containers in predefined places in turn requiring more thought in preparation for a staining run.

Ability to process more tissue samples without reprogramming

In a laboratory context, processing of large numbers of samples is important. However, prior art systems, such as Stark, assigned a particular staining protocol to a slide position. (*e.g.*, position 1 was

programmed with sequence 1, position 2 was programmed with sequence 2, etc.). However, this type of arrangement is very inflexible, potentially resulting in failing to use all of the available positions in the slide support for staining. For example, if the technician wishes to stain all of the slides with sequence 1, yet slide position 2 is programmed with sequence 2, either the technician does not use slide position 2 or the programming must be changed. More than likely, the programming will not be changed, resulting in a failure to maximize the use of the staining module. With automated processing, the system is flexible. All of the positions in a staining system may be used during every run, thereby maximizing the ability to process tissue samples.

In summary, Stark et al., Sakurada and Saralegui et al. taken alone or in any combination, do not teach or suggest an apparatus having identification of the reagent container or determining whether reagent in the reagent container should be dispensed onto the slide in the particular configuration that Applicants particularly disclose and claim. Therefore, the Examiner has not established prima facie obviousness over Stark et al. in combination with Sakurada or Stark et al. in combination with Saralegui et al. and the rejections under 35 U.S.C. §103(a) should be withdrawn. Applicants respectfully request reconsideration of the application on that basis.

Rejection based on Stark, Sakurada, Saralegui and Rokugawa references

In Paragraph 10 of the Office Action, claims 84, 94-98 and 105-106 were rejected under 35 U.S.C. §103 as being unpatentable over Stark et al. (J. Immunol. Methods 107:89-92 (1988)) in view of Sakurada (U.S. Patent No. 4,346,056) or Saralegui et al. (U.S. Patent No. 5,439,645), and further in view of Rokugawa (U.S. Patent No. 4,844,868).

The Examiner asserted that the Stark, Sakurada and Saralegui references failed to recite the step of moving the reagent container and slide support relative to one another to position the reagent over the

slide. The Examiner further asserted that the Rokugawa reference teaches a method and apparatus for delivering reagents to reaction containers wherein a plurality of reagents 68 are supported on a reagent carousel 64 over a reaction carousel.

As discussed previously, the Stark, Sakurada and Saralegui references alone or in combination do not render the claims obvious. Likewise, the Rokugawa reference does not teach, or even suggest, the invention as claimed. The Rokugawa reference does not teach, or even suggest the use of bar coding, or any other form of automatic identification of the reagent containers or automatic determination of whether reagent should be dispensed onto the slide. In contrast, Claim 72 (upon which claim 84 ultimately depends) includes the limitations of "automatically identifying the reagent container using a computer" and "automatically determining whether reagent in the reagent container should be dispensed onto the slide". Likewise, claim 94 includes the limitations of "automatically identifying the reagent container using a computer" and "automatically determining whether the reagent in the reagent container should be dispensed onto the slide". Finally, claim 99 (upon which claims 105 and 106 ultimately depend) includes the limitation of "the bar code reader reads reagent bar codes on the reagent containers and wherein the reagent bar codes are sent to the computer for automatically identifying the reagent containers". Therefore, applicants believe that the Stark, Sakurada, Saralegui and Rokugawa references, taken alone or in combination, do not render the claims obvious.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the presently pending claims in the application are believed to be in condition for allowance and patentably distinguish over the art of record. An early notice thereof is earnestly solicited.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: June 26, 2001

By: _____
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APPENDIX UNDER 37 CFR 1.121(c)

81. (Amended) The method of claim 80 wherein the slide bar code identifies a slide sample placed on the slide and identifies a [histochemical process] sequence of reagents for the slide sample.

88. (Amended) A method of dispensing reagents onto a slide, the method comprising the steps of:

providing a plurality of reagent containers in a reagent support, each of the reagent containers having a reagent barcode;

providing slides on a slide support, the slides having at least one slide bar code;

providing a bar code reader;

reading the bar codes on the reagent containers;

determining reagents in the reagent containers based upon the reading of the bar codes on the reagent containers;

reading the slide bar [code] codes on the slides;

determining a sequence of reagents to be applied on the slides based upon the reading of the slide bar [code] codes on the slides; and

dispensing the reagents in the reagent containers based upon the sequence of reagents to be applied.

94. (Amended) A method of dispensing reagents onto a slide, the method comprising the steps of:

providing at least one reagent container;

providing at least one slide on a slide support;

automatically identifying the reagent container using a computer;

automatically determining whether the reagent in the reagent container should be dispensed onto the slide;

moving the reagent container and the slide support relative to one another to position the reagent container over the slide; and

dispensing the reagent in the reagent container onto the slide based on the determination of whether the reagent in the reagent container should be dispensed onto the slide.

99. (Amended) An automated biological staining apparatus comprising:

a slide support for holding slides;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

bar code reader;

reagent dispensing device for applying reagent onto a particular slide; and

computer in communication with the slide support drive means, the reagent drive means, [and] bar code reader and means for dispensing reagent,

wherein the bar code reader reads reagent bar codes on the reagent containers and slide bar codes on the slides, and

wherein [the reagent bar codes are sent to] the computer [for] automatically [identifying] determines whether reagent in the reagent containers should be dispensed onto the particular slide.

103. (Amended) The automated biological staining apparatus of claim 99 wherein the bar code reader reads slide bar codes on the slides and wherein the slide bar codes are sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the [slides] particular slide.

104. (Amended) The automated biological staining apparatus of claim 99 further comprising:

homing device connected to the slide support and in communication with the computer wherein the homing device determines position information for the [slides] particular slide.

105. (Amended) The automated biological staining apparatus of claim 99 wherein the computer controls the movement of [moves] the reagent tray and the slide support to move relative to one another to position the reagent containers over the [slides] particular slide.

107. (Amended) An automated biological staining apparatus comprising:

a slide support for holding slides;

slide support drive means for moving the slide support;

a reagent tray for supporting reagent containers;

reagent drive means for moving the reagent tray;

means for automatically identifying the reagent containers;

means for automatically determining whether reagent in the reagent containers should be dispensed onto [the] a particular slide; and

reagent dispensing device for applying reagent onto a particular slide

[computer in communication with the slide support drive means, the reagent drive means, the means for automatically identifying the reagent containers, and the means for automatically determining whether reagent in the reagent containers should be dispensed onto the slide].

109. (Amended) The automated biological staining apparatus of claim 107 wherein means for automatically determining whether reagent in the reagent containers should be dispensed onto the slide includes a bar code reader, wherein the bar code reader reads slide bar codes on the slides and wherein the slide bar codes are sent to the computer for automatically determining whether reagent in the reagent containers should be dispensed onto the [slides] particular slide.

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September 26, 2005

Via Federal Express

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Re: Ventana Medical Systems, Inc. v. Vision BioSystems Inc.
District of Mass. 05-CV-10614-GAO
Our Ref.: 2961-102

Dear Nicole:

Enclosed is Bond Service Manual 21.7509.500 Revision: DRAFT (C01_2) with printed comments bearing production numbers VBS-OCR 077512 - VBS-OCR 078687.

If you have any questions please feel free to contact Ms. Leff.

Very truly yours,

Nasri V. B. Hage

NVH:tbm

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